What is the effect of paracetamol (acetaminophen) ingestion on exercise performance? current findings and future research directions

What is the effect of paracetamol (acetaminophen) ingestion on exercise performance? Current findings and future research directions

Jozo Grgic[1]

[1]Institute for Health and Sport, Victoria University, Melbourne, Australia

Corresponding author:

Jozo Grgic

Email: jozo.grgic@live.vu.edu.au

Abstract

In recent years, studies have explored the effects of paracetamol (acetaminophen) ingestion on exercise performance. However, due to the contrasting findings, there is still no consensus on this topic. This article provides an overview of the effects of paracetamol on endurance, sprinting, and resistance exercise performance. Studies have reported that paracetamol ingestion may be ergogenic for endurance performance. These effects occur when paracetamol is ingested 45 to 60 min before exercise and appear to be more pronounced in time-to-exhaustion vs. time-trial tests. Besides endurance, paracetamol ingestion 30 min before exercise increases mean power during repeated cycling sprints in interval training involving repeated 30-s all-out bouts. Preliminary data on paracetamol ingestion also suggest: (a) improved endurance performance in the heat; (b) an improvement in single sprint performance, at least when paracetamol is ingested following exercise-induced fatigue; and (c) attenuation of the decline in muscular strength that occurs with repeated maximum contractions. An ergogenic effect of paracetamol is most commonly observed when a dose of 1500 mg is ingested 30 to 60 min before exercise. Despite these performance-enhancing effects, the aim of this article is not to promote paracetamol use, as side effects associated with its consumption and ethical aspects need to be considered before utilizing paracetamol as an ergogenic aid. Future research on this topic is still needed, particularly related to paracetamol dosing, timing of ingestion, and the effects of paracetamol in females and elite athletes.

Key points:

1. Currently available studies indicate that paracetamol may be ergogenic for endurance, sprinting, and resistance exercise performance.
2. An ergogenic effect of paracetamol is most commonly observed when a dose of 1500 mg is ingested 30 to 60 min before exercise.
3. Before utilizing paracetamol as an ergogenic aid, a careful analysis of different ethical aspects and side effects associated with its consumption needs to be performed.

1. Introduction

Paracetamol (acetaminophen) is among the most commonly used medications for pain relief and fever reduction [1, 2]. Paracetamol decreases pain perception due to the inhibition of prostaglandin synthesis [3]. The inhibition of prostaglandin synthesis reduces transduction of the sensory nerves and decreases nociceptive impulse transmission, likely explaining paracetamol's effects on pain modulation [3, 4]. Much of the pharmacology and toxicology of paracetamol is similar to non-steroidal anti-inflammatory drugs (NSAID; e.g., ibuprofen) [3]. However, paracetamol is not considered an NSAID, given that it only has weak anti-inflammatory activity [3]. While paracetamol is consumed in the general population, studies also observed that this medication is used among athletes [5-8]. Athletes generally report using paracetamol to decrease pain from a previous exercise bout [9]. However, less is currently known about the use of paracetamol for acute improvements in performance [10, 11].

Pain perception may play an important role in different modes of exercise [12]. For example, data indicate that exercise-induced pain tolerance is significantly correlated with cycling performance (r = 0.83) [13]. Acute muscle pain also occurs during other forms of exercise, such as sprinting and resistance exercise [14, 15]. Muscle pain may alter the brain's ability to recruit muscle fibers to produce force, contributing to decreased performance [16]. From a psychological perspective, it is also important to emphasize that perceived pain drives the individual to disengage with the behavior/action causing it [17]. Theoretically, reducing exercise-induced pain may help to improve performance [18]. Indeed, this notion is supported by data indicating that transcutaneous electrical nerve stimulation reduces exercise-induced pain, which contributes to improvements in exercise performance [17]. Due to its hypoalgesic effects, similar effects may be expected with paracetamol ingestion. While studies have explored the effects of acute paracetamol ingestion on exercise performance, there is still no consensus on this topic due to the conflicting reports [15, 19-34].

In recent years, there has been growing interest in exploring sex differences in the physiology of exercise [35]. Compared to men, women generally have increased pain sensitivity [36]. Some of these sex-based differences in pain perception are likely explained by the anatomic differences in the organization of pain-signaling pathways and the influence of sex hormones

on these pathways [36]. Additionally, data indicate that the pharmacokinetics of paracetamol (peak plasma concentration and time to reach the peak concentration) differ between men and women [37]. Thus, besides the interest in exploring the overall effects of paracetamol on exercise performance, there is also interest in researching if paracetamol's effects vary between sexes. Therefore, the present article aims to: (i) provide an overview of the current findings on the effects of paracetamol ingestion on exercise performance; (ii) evaluate if these effects are sex-specific; and (iii) highlight key areas that warrant exploration in future studies.

2. Effects of paracetamol on exercise performance

2.1 Endurance performance

From an exercise standpoint, the effects of paracetamol ingestion on endurance performance have received the most attention in the literature. The first study [24] on this topic utilized a cycling time-trial task to evaluate endurance performance. Researchers found that ingesting 1500 mg of paracetamol 60 min before exercise reduced the time needed to complete 16.1-km cycling by 30 s [24]. These results seemed highly promising at the time, given that the ergogenic effects of paracetamol found in this study (Cohen's d = 0.27; 1.9%) were similar to the effects of other, well-established ergogenic aids such as caffeine and sodium bicarbonate [38-41]. However, despite these initial findings, studies in the years to come reported more conflicting data. For example, two studies [22, 33] also used cycling time-trials to evaluate endurance performance while providing paracetamol in relative (20 mg/kg of body mass) or absolute (1500 mg) doses 60 min before exercise. These two studies did not find an ergogenic effect of paracetamol ingestion on endurance performance in 6-min or 4-km cycling. Thus, until recently, there was no consensus on the use of paracetamol as an ergogenic aid for endurance performance.

In 2021, Grgic and Mikulic published a meta-analysis examining the effects of paracetamol on endurance performance [42]. Besides exploring the overall effects, the analysis also examined the influence of moderating factors such as the timing of paracetamol ingestion and the effects in different endurance tests (i.e., time-to-exhaustion vs. time-trial). This meta-analysis included ten randomized, double-blind studies [19, 20, 22, 24, 25, 28-30, 33, 34]. When pooling the data from all included studies, there was no significant difference between

placebo and paracetamol (Cohen's *d* = 0.09; 95% confidence interval [CI]: –0.04, 0.22). However, in a subgroup meta-analysis that explored the influence of ingestion timing, it was found that paracetamol was ergogenic when it was consumed 45 to 60 min before exercise (Cohen's *d* = 0.14; 95% CI: 0.07, 0.21; 4.5%). These findings have support from a physiological standpoint, given that the plasma paracetamol half-life is estimated to be from 1.5 to 2.5 h [43, 44]. Therefore, the optimal timing of paracetamol ingestion is likely to be around 45 to 60 min before exercise. Based on these findings, it seems reasonable to suggest that the exercise bout should coincide with paracetamol peak plasma levels to increase the likelihood of an ergogenic effect.

Additionally, it was found that paracetamol was ergogenic when consumed before time-to-exhaustion endurance tests (Cohen's *d* = 0.19; 95% CI: 0.06, 0.33; 8.8%) [42]. However, there was no significant difference between placebo and paracetamol for endurance performance in time-trials. As suggested by the name, in time-to-exhaustion tests, the task is to continue with the exercise test until complete exhaustion occurs. In time-trials, the participants must complete a set distance (e.g., 4 km) as soon as possible or cover the most distance during a fixed time period (e.g., 6 min). Due to their structure differences, it was hypothesized that time-to-exhaustion tests might produce higher levels of acute pain—particularly in the later stages of the test—which could explain these findings. However, out of the analyzed studies, only Mauger et al. [24] evaluated pain perception during a 16.1 km time-trial and reported that it was from 3 to 7, on a 0 to 10 point scale. None of the studies [19, 20, 25, 30] that used time-to-exhaustion tests evaluated pain perception, thus preventing any direct comparisons. One study [45] compared cycling performance in time-to-exhaustion and time-trials where the duration of the trials was matched, and the participants were blinded to elapsed time and power output. Interestingly, the study found a higher average power output in the time-to-exhaustion vs. time-trial tests (294 vs. 282 W). This might suggest that participants approach their physiological limit in time-to-exhaustion tests, which is why they would benefit more from the paracetamol stimulus. Still, this hypothesis remains to be tested in future studies.

Overall, based on the current body of evidence, it seems that paracetamol may enhance endurance performance. These effects occur when paracetamol is ingested 45 to 60 min

before exercise. Additionally, data currently suggest a benefit of paracetamol ingestion in time-to-exhaustion endurance tests but not in time-trials.

2.2 Endurance performance in the heat

The use of paracetamol as an antipyretic to treat fever is well-established [3]. Paracetamol ingestion has also been reported to reduce the core temperature in normothermic, non-febrile humans [46]. Such an effect is not likely to contribute to improved exercise performance in temperate conditions [47]. However, given that reducing body temperature using strategies such as pre-cooling may enhance performance during hot conditions, paracetamol ingestion may also be ergogenic during exercise in the heat [48]. One study [49] provided 20 mg/kg of paracetamol 60 min before cycling exercise at a fixed rate in the heat (34.5°C, 52% of relative humidity). Paracetamol ingestion did not affect physiologic thermoregulatory control as there was no significant difference for rectal, esophageal, and skin temperature. However, it should be considered that this study only evaluated physiological outcomes without focusing on exercise performance.

In one study that evaluated changes in temperature and exercise performance, Mauger et al. [25] demonstrated that paracetamol ingestion (20 mg/kg of lean body mass) increased time-to-exhaustion during cycling in the heat (30°C, 50% of relative humidity). Specifically, the participants cycled 4 min longer when they consumed paracetamol (placebo: 19 ± 13 min vs. paracetamol: 23 ± 15 min). This increase in performance was coupled with lower core (–0.15°C), skin (–0.47°C), and body (–0.19°C) temperatures. These findings, however, were not fully replicated by another study. Burtscher et al. [19] explored the effects of paracetamol (500 mg 120 min before exercise) on running time-to-exhaustion at 30°C. It was observed that the increase in core temperature after 20 min of running was lower in the paracetamol trial. However, there was no significant difference between paracetamol and placebo in running time. Still, the effects favored the paracetamol trial, given that an average increase in running time of 2.3 min was observed (paracetamol: 47.5 ± 15.5 min vs. placebo: 45.2 ± 13.1 min; Cohen's *d*: 0.15; 5.1%). This should be considered as even small performance improvements may be worthwhile in competitive sport, where narrow margins commonly determine placings [50, 51]. As the effects favored the paracetamol condition, the lack of significant findings in this study might have been due to the small sample size (n = 7). Additionally, this

study provided paracetamol in the dose of 500 mg 120 min before exercise, which is not likely to be the optimal protocol of supplementation [42].

In summary, there is evidence to suggest a potential benefit of paracetamol on endurance performance in the heat, which is likely mediated by its antipyretic effects [3, 25]. Still, there is also a clear need for more studies on the topic.

2.3 Sprint performance

While most studies focused on outcomes related to endurance performance, several studies explored the effects of paracetamol on sprint performance [15, 21, 23, 31]. Most of these studies evaluated the effects of paracetamol on sprint interval training, involving 30-s all-out bouts interspersed with 2 to 4-min rest [15, 21, 31]. The effects of paracetamol on sprint interval training are likely to be of substantial practical importance given that this type of training has become increasingly popular due to its time-efficiency and comparable effectiveness on physiological adaptations as high volume endurance training [52, 53].

Foster et al. [15] included nine active male participants who ingested 1500 mg of paracetamol or placebo 30 min before exercise. The exercise session was highly fatiguing as it involved 8 bouts of the Wingate test (30-s all-out cycling) interspersed with 2-min rest. Results indicated that paracetamol ingestion increased mean power throughout the 8 Wingate bouts by 5%. Further analyses demonstrated that this increase in mean power was attributed to higher power output in Wingate bouts 6–8 (10–11%). Delextrat et al. [21] used the same exercise and supplementation protocol but included females as study participants. An increase in mean power (~6%) over 8 Wingate bouts was observed. More specifically, higher mean power values were found in bouts 2, 3, and 5 (11–13%). Additionally, peak power was 14% higher in the paracetamol trial, but only in bout 5.

One study [31] used a very similar protocol, where male participants ingested 1500 mg of paracetamol or placebo 40 min before 8 bouts of 30-s all-out running on a treadmill (2-min rest between bouts). However, paracetamol was not found to be ergogenic. Tomazin et al.

[54] compared the physiological effects of repeated sprints in running and cycling. Central fatigue was found only after running, suggesting that it may limit performance in this exercise modality [54]. Paracetamol ingestion does not appear to affect central fatigue [27], which might explain why there was no ergogenic effect of paracetamol on performance in interval running. When performing repeated cycling sprints, an increase in power output has been associated with increased muscle activation [55]. This is relevant to consider, as paracetamol ingestion may increase muscle activation [27] and contribute to its ergogenic effect in cycling sprints. However, as only one study [31] used a running-based protocol, future studies are needed to explore the effects of paracetamol on performance in interval running.

In all three analyzed studies [15, 21, 31], paracetamol ingestion was not ergogenic in the first sprint. These results suggest that paracetamol enhances performance in repeated but not in single sprints. However, single sprint performance may be enhanced with paracetamol ingestion, provided that it is consumed in an exercise-fatigued state [23]. One study [23] included 17 participants, who first performed 3 × 300-m running (5 to 10 min-rest between bouts). Immediately after interval running, the participants ingested 500–750 mg of paracetamol. Then, 35 min after ingestion, they performed a 60-m sprint. Compared to placebo, paracetamol reduced the time needed to complete the sprint by 0.5 s, coupled with higher perceived recovery. Further analyses for sex-specific effects revealed that the improvements in sprint performance were similar in males (0.5 s) and females (0.45 s).

Overall, currently available studies suggest that ingesting 1500 mg of paracetamol 30 min before exercise may enhance repeated cycling sprint performance. Specifically, it seems that paracetamol effectively attenuates the decline in power output in repeated sprints. In addition, preliminary data also suggest that paracetamol ingestion may enhance single sprint performance, at least if ingested in a fatigued state.

2.4 Resistance exercise performance

Out of the different exercise modes, the effects of paracetamol on resistance exercise performance have received the least attention. This is surprising given that resistance exercise—especially when performed to muscular failure—has been reported to induce high

levels of acute pain [14]. One study reported that paracetamol (1000 mg 45 min before exercise) did not increase time to failure in isokinetic knee extension [26]. Another study [27] explored the effects of paracetamol (1000 mg 60 min before exercise) on torque during 60 × 3-s maximum voluntary contractions separated by a 2-s passive recovery period. Mean torque and critical torque were 3% and 4% higher following paracetamol ingestion, respectively [27]. This improvement in performance was attributed to higher levels of muscle activation, as the electromyography amplitude at the end of the exercise was 28% higher in the paracetamol trial. Paracetamol ingestion has also been reported to increase motor evoked potential, which might also contribute to improvements in performance [56]. These preliminary findings suggest that paracetamol may attenuate the decline in muscle strength that occurs with repeated contractions. This finding may be of relevance given that attenuating the decline in force production during multiple sets has been found to contribute to greater gains in strength [57].

Additionally, based on the torque values, it would seem that paracetamol ingestion allows for higher force production throughout the resistance exercise session [27]. In essence, paracetamol ingestion enhances the 'quality' repetitions (i.e., higher force/velocity), which needs to be placed into the context of findings reported in velocity-based studies [58, 59]. For example, one study that utilized velocity-based training found that exercising at a 20% velocity loss produced greater gains in vertical jump height than training at a 40% velocity loss [58]. This advantage was observed even though the 20% velocity loss group performed 40% fewer repetitions. Still, while studies that explored the effects of paracetamol on outcomes such as muscular endurance and strength provide valuable mechanistic insights, their utilized protocols do not necessarily mirror 'real-world' resistance exercise sessions, where several sets of different exercises are performed using eccentric and concentric muscle actions at a given percentage of maximum strength [60]. Therefore, this gap should be addressed in future studies.

3. Interaction of paracetamol with other supplements

Due to the ergogenic potential of paracetamol, studies have explored its interaction with other supplements. For example, two studies [22, 33] examined the effects of paracetamol combined with caffeine on endurance performance. Caffeine is commonly added to

analgesics, such as paracetamol [61]. The addition of caffeine to analgesics has been reported to have additive effects for pain relief [61]. The combination of paracetamol and caffeine is interesting given that caffeine primarily acts by binding to adenosine receptors, subsequently reducing perceived exertion/pain and improving performance [62, 63]. Therefore, it seems that caffeine and paracetamol may improve performance through similar mechanisms. However, in both studies that explored this supplement combination, ergogenic effects were observed when isolated caffeine was ingested or combined with paracetamol [22, 33]. Both studies used cycling time-trials to evaluate endurance performance, which is relevant if we consider the meta-analytical data suggesting ergogenic effects of paracetamol on endurance performance in time-to-exhaustion but not time-trial tests [42]. Caffeine, however, has well-established ergogenic effects for endurance performance in time-trials [38, 39], which might explain the findings in these two studies.

One study explored the effects of combining paracetamol and acetylsalicylic acid (aspirin) on exercise performance [32]. A combination of paracetamol (500 mg) and aspirin (500 mg) was provided to 16 participants 40 min before evaluating Wingate test performance. There was no significant difference in Wingate test performance between the experimental (i.e., paracetamol and aspirin) and placebo trials in this study. However, several aspects of the study design need to be mentioned. First, the dose of paracetamol was small (500 mg). Also, a single Wingate was used to evaluate performance, which is relevant given that currently available studies suggest that paracetamol ingestion is ergogenic in repeated Wingate sprints (see section 2.2). Additionally, only two trials (i.e., paracetamol and aspirin vs. placebo) were incorporated, not providing insights into the isolated effects of paracetamol and aspirin. Finally, researchers interested in exploring the combined effects of paracetamol with other medications/supplements should focus on those aids that already have established ergogenic effects. This does not seem to be the case with aspirin, as several studies reported that this medication does not enhance exercise performance [64-66].

4. Side effects

As with any drug/supplement, side effects associated with its consumption need to be considered. Out of the studies analyzed herein, none reported any side effects associated with paracetamol ingestion. However, it is also unclear if there was a comprehensive attempt to

record all possible side effects. Previous studies have reported that paracetamol may negatively affect anabolic signaling and decrease muscle protein synthesis in young adults [67, 68]. Still, these effects may be age-dependent, given the data reporting a positive effect of paracetamol ingestion on muscular hypertrophy among older adults (64 ± 1 years) [70]. When ingested at recommended doses, paracetamol is generally considered to be safe [3]. Still, paracetamol overdose is also one of the most common causes of liver failure in some countries [70]. While liver failure generally occurs with doses of 7 g or higher (well above the doses needed for an ergogenic effect), due to potential hepatotoxicity, paracetamol use as an ergogenic aid should likely be infrequent and with caution [70]. Paracetamol is currently not prohibited by the World Anti-Doping Agency, even though some have suggested it should be included in the class of substances subjected to Therapeutic Use Exemption [71]. Ethical aspects of using paracetamol among athletes also need to be considered, as those using medication to reduce pain sensations might be at a greater risk of injury (or re-injury) and tissue damage [10]. A careful analysis of these aspects needs to be performed before using paracetamol as an ergogenic aid.

5. Areas for future research

Based on the overview of the current evidence, several key areas for future research are identified:

1. Studies that explored the effects of paracetamol on exercise performance included either recreationally active individuals or competitive athletes (Table 1); none of the studies included elite athletes as participants. Given that athletes have higher pain thresholds than non-athletes [72, 73], paracetamol may be less likely to be ergogenic in this cohort. However, it could also be hypothesized that elite athletes are likely to be even more responsive to paracetamol as they possess the mental discipline to exercise long/hard enough to benefit more from the paracetamol-induced pain reduction. Future research is needed to provide clarity on this topic.
2. Future studies should also seek to explore the effects of paracetamol on exercise performance in females. This topic needs to be further examined, given that women have increased pain sensitivity and might also respond differently to paracetamol [74]. For some outcomes (e.g., endurance), studies published thus far only included males as participants [42]. In the studies that focused on sprint performance, one included

females and reported an ergogenic effect, while another observed similar improvements in performance among both males and females [21, 23]. These initial findings suggest that there might not be a sex-specific response to paracetamol's effect, but more research is needed.

3. The most commonly used dose of paracetamol is 1500 mg. However, no dose-response studies have examined the 'optimal' dose of paracetamol for exercise performance. This is one of the key areas needing focus in future studies, given that paracetamol bioavailability is dose-dependent [43].
4. In addition to the dose, studies are also needed on the timing of paracetamol ingestion. Meta-analytical data reported that the timing of paracetamol ingestion is important, with ergogenic effects observed when paracetamol is consumed 45 to 60 min before exercise [42]. Other studies used 30 min as the timing of paracetamol ingestion and reported an ergogenic effect, likely due to paracetamol plasma half-life (1.5 to 2.5 h) [15, 21, 23]. Data are also reporting that meaningful pain relief occurs ~35 min post-ingestion, highlighting the importance of paracetamol timing [75]. Future studies are needed to directly explore the effects of paracetamol ingestion timing on exercise performance.
5. Finally, more research is needed on mechanisms underpinning the ergogenic effect of paracetamol. Given that this medication is primarily used for pain relief, it seems likely that a reduction in pain perception is responsible for improvements in performance following paracetamol ingestion. However, one study reported a reduction in pain perception with no improvements in performance [31]. Other studies [15, 24] reported ergogenic effects that were not accompanied by changes in pain perception. Despite no significant differences in pain perception, these studies [15, 24] still observed higher power output for the same pain sensation. Due to the conflicting findings, more work on mechanisms is needed.

While not exhaustive, it is hoped that some of the suggestions herein will catalyze future high-quality studies on this topic.

6. Conclusions

Currently available studies indicate that paracetamol may be ergogenic for endurance performance when ingested 45 to 60 min before exercise. An ergogenic effect is also observed

in time-to-exhaustion but not time-trial endurance tests. Paracetamol ingestion 30 min before exercise also increases mean power during repeated cycling sprints in interval training. Preliminary data on paracetamol ingestion also suggest: (a) improved endurance performance in the heat; (b) an improvement in single sprint performance, at least when paracetamol is ingested following exercise-induced fatigue; and (c) attenuation of the decline in muscular strength that occurs with repeated maximum contractions. An ergogenic effect of paracetamol is most commonly observed when a dose of 1500 mg is ingested 30 to 60 min before exercise. Despite these performance-enhancing effects, the aim of this article is not to promote paracetamol use, as side effects associated with its consumption and ethical aspects need to be considered before utilizing paracetamol as an ergogenic aid. Future research on this topic is still needed, particularly related to paracetamol dosing, timing of ingestion, and the effects of paracetamol in females and elite athletes.

Ethics declarations

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