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Title page

Title

The haemodynamic effects of intravenous paracetamol (acetaminophen) in healthy volunteers: a double-blinded, randomized, triple crossover trial

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Running Head

Haemodynamic effects of IV paracetamol (acetaminophen) in healthy volunteers

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Summary

Introduction

The haemodynamic effects of intravenous paracetamol have not been systematically investigated. We compared the physiological effects of intravenous mannitol-containing paracetamol, and an equivalent dosage of mannitol, and normal saline 0.9% (NS) in healthy volunteers.

Methods

We performed a blinded, triple crossover, randomized trial of 24 adult healthy volunteers. Participants received IV paracetamol (1 g paracetamol + 3.91 g mannitol/100 mL), IV mannitol (3.91 g mannitol/100 mL), and IV NS (100 mL). Composite primary end points were changes in mean arterial pressure (MAP), systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured pre-infusion, during a 15 minute infusion period, and over a 45 minute observation period. Systemic vascular resistance index (SVRI), cardiac index (CI) were measured at the same time points.

Results

Infusion of paracetamol induced a transient yet significant decrease in blood pressures from pre-infusion values (MAP -1.85mmHg (95% CI: -2.6 to -1.1), SBP -0.54mmHg (95% CI: -1.7 to 0.6) and DBP -1.92mmHg (95% CI: -2.6 to -1.2); $p<0.0001$), associated with a transient reduction in SVRI and an increase in CI. Changes were observed, but to a lesser extent with NS (MAP -0.15mmHg, SBP +1.44mmHg, DBP -0.73mmHg $p<0.0001$), but not with mannitol (MAP +1.47mmHg, SBP +4.03mmHg, DBP +0.48mmHg; $p<0.0001$).

Conclusions

IV paracetamol caused a transient decrease in blood pressures immediately after infusion. These effects were not seen with mannitol or NS. The physiological mechanism was consistent with vasodilatation. This study provides plausible physiological data in a healthy volunteer setting, supporting transient changes in haemodynamic variables with IV paracetamol and justifies controlled studies in the peri-operative and critical care setting.

What is known about this subject?

IV paracetamol is ubiquitous in critical care and perioperative medicine. IV paracetamol formulations that are manufactured by major pharmaceutical companies contain as much as

3.91g of mannitol per dose of 1g/100mL IV paracetamol. It is unknown if the IV formulations are associated with transient hypotension.

What the study adds

In a healthy volunteer model, IV paracetamol caused a transient decrease in blood pressure immediately after infusion. The physiological mechanism was consistent with vasodilatation. These haemodynamic effects were transient and of small magnitude, however may have a different intensity and duration in patients who are critically ill.

Body Text

Introduction

Paracetamol (also known as acetaminophen) is ubiquitously used in hospitals as an antipyretic and analgesic. It is frequently administered intravenously (IV) to patients undergoing major surgery and to critically ill patients, where oral intake and rectal suppositories may not be possible [1]. Paracetamol has negligible solubility in aqueous solutions. Mannitol on the other hand, is commonly used in IV paracetamol formulations as a stabilizing compound. The inclusion of mannitol in IV paracetamol is not widely appreciated. IV paracetamol formulations that are manufactured by major pharmaceutical companies contain as much as 3.91g of mannitol

per dose of 1 g/100 mL IV paracetamol. Bristol-Myers Squibb, Cadence Pharmaceuticals and Actavis Pharmaceuticals use mannitol as a stabilizing compound, while Pfizer has produced a non-mannitol containing formulation.

IV paracetamol is widely believed to be safe and free of adverse effects. However, with growing use concerns have developed in critical care literature, which suggests that IV formulations may be associated with transient hypotension [1-8]. Additionally, studies examining the haemodynamic effects of IV paracetamol are notably limited by their retrospective design, small patient numbers, and lack of randomization and blinding. No studies have investigated these putative adverse effects in the absence of disease-related confounders in a healthy volunteers setting or tested whether its main excipient (mannitol) contributes to such effects. We hypothesized that the IV paracetamol formulation (3.91 g mannitol + 1 g paracetamol/100 mL) would lower blood pressure in healthy volunteers when compared to IV mannitol (3.91 g/100 mL) or 0.9% Normal Saline (NS) (100 mL) (placebo), and conducted a double-blinded, randomized, triple crossover study to test our hypothesis.

Methods

The Austin Health Research and Ethics Committee approved this study (number: 05005/2013) and all patients gave written informed consent. We registered the study with the Australian New Zealand Clinical Trials Registry (number: 12615000533594). Between October 2013 and April 2014 we recruited participants by word of mouth from perioperative medical personnel at the Austin Hospital, a large University-affiliated, metropolitan hospital in Melbourne, Australia. Inclusion criteria included normotensive healthy participants, on no medications, and between 18 and 60 years of age. Exclusion criteria included requirement for any chronic medications, pregnancy, body mass index greater than 35 kg/m^2 , intellectual disability, known history of liver and/or renal impairment, previous allergy to the study drugs, consumption of caffeine within 12 hours of each experiment, and consumption of NSAID or paracetamol containing products within 24 hours of each experiment.

The primary composite end points were changes in mean arterial pressure (MAP), systolic blood pressure (SBP) and diastolic blood pressure (DBP) pre-infusion, during a 15 minute infusion period, and then post-infusion during a 45 minute observation period. Other variables collected at the same time points included systemic vascular resistance index (SVRI), cardiac index (CI), stroke volume index (SVI), heart rate (HR), and plasma osmolality. Normal reference values for these end points were: MAP: 70-105 mmHg; SBP: 100-140; DBP: 60-90 mmHg; SVRI: 1970-2395 mmHg/L/min/m²; CI: 2.5-4.0 L/min/m²; SVI: 33-47 ml/m²/beat; HR: 60-90 b/min, plasma osmolality: 275-295 mOsm/kg.

Analytical Methods

All continuous beat-to-beat haemodynamic variables were measured with the fourth generation non-invasive Edwards Lifesciences Nexfin™ system, which uses the volume clamp method [9] to continuously measure blood pressure (MAP, SBP and DBP), and the physiological method [10] for initial and continuous calibration. Real-time reconstruction of the blood pressure waveform allowed computation of stroke volume, cardiac output, systemic vascular resistance, and dP/dt using a pulse contour method. Blood pressure measurements with Nexfin™ technology has been reported as being more accurate than traditional upper arm blood pressure cuff [11, 12], is approved by the Association for the Advancement of Medical Instrumentation criteria [13] and is validated against intermittent non-invasive [14] and continuous invasive methods [15].

Currently there is no reliable assay to determine the level of mannitol in plasma or serum, nor any biochemical indicator or metric to measure the potential haemodynamic effects of mannitol in plasma. Being an osmotic diuretic that is filtered at the glomerulus yet not significantly reabsorbed in the proximal tubule, mannitol acutely raises plasma/extracellular osmolality. In order to quantify any diuretic effects of mannitol on osmolality, plasma osmolality was measured by placing a tourniquet on the arm for blood sampling: 5 mL of blood was taken and discarded, followed by a 3 mL sample for plasma osmolality in a 6 mL lithium-heparin blood Vacuette® (Greiner bio-one, Kremsmünster, Austria). Plasma osmolality was measured with an

Advanced® Model 3300 Micro-Osmometer (Advanced Instruments, Inc., Norwood, Massachusetts, United States of America). This device calculates osmolality via Freezing Point Depression Osmometry by measuring the total molar concentration of dissolved solids in any solution.

Standardization of setting

Participants attended on 3 separate trial days with a washout period between trial days of between 24 hours and one week. All participants were fasted for solid foods for 6 hours and 2 hours for clear liquids prior to each experiment. On arrival, participants were encouraged to empty their bladders to avoid discomfort during the study. The study was conducted in a dedicated research laboratory with standardized of illumination intensity and noise, and with ambient air temperature set to 21⁰C to avoid distractions that may alter haemodynamics during the continuous measurements.

Participants were placed in a supine position on a standard hospital bed with their heads raised at 45 degrees and resting on a pillow for comfort. The finger cuff of the Nexfin™ was placed on the middle phalanx of the index finger of the dominant hand. Stable baseline measurements were observed prior to each study arm in pre-study monitoring over a period of 10 minutes. Stable baseline measurements were observed prior to each study arm in pre-study monitoring over a period of 10 minutes. A 22-gauge Introcan Safety® intravenous cannula (Braun, Melsungen,

Germany) was placed either in the peripheral veins located on the back of the non-dominant hand or the cubital fossa of the non-dominant arm. A Safsite® injection site safety connector was fitted for the IV infusion set and blood sampling. After the insertion of the cannula, blood pressure was allowed to stabilize to baseline values over a further 10 minute period. At the end of this time period, continuous haemodynamics were recorded for a period of 2 minutes to capture stable baseline haemodynamic variables. Participants then received IV paracetamol (1 g paracetamol + 3.91 g mannitol/100 mL) (Actavis Australia, The Rocks, NSW, Australia), IV mannitol (3.91 g mannitol/100 mL) (Baxter Healthcare, Toongabbie, NSW, Australia) or IV NS (100 mL) as placebo (Baxter Healthcare, Toongabbie, NSW, Australia). The composition of 100 mL Actavis formulation of IV paracetamol includes paracetamol 1000 mg, mannitol 3910 mg in the following stabilisers - cysteine hydrochloride monohydrate, dibasic dehydrate sodium phosphate, sodium hydroxide, hydrochloric acid and water for injection. Study drugs were infused at room temperature via a volumetric pump (Alaris GP; Cardinal Health, Seven Hills, NSW, Australia) over 15 minutes. The cannula and Edwards Lifesciences Nexfin™ finger cuff were removed at the end of the study period. Participants were assigned to receive all three treatments in randomly allocated orders via a computer generated randomization program without blocking, stratification or other restrictions.

Blinding

Participants received their own unique randomization code using a computer generated randomization program (www.randomization.com). Random permutations of treatments for each subject were created using the randomization program second generator application (Seed number: 203), and entering “Paracetamol”, “Mannitol” and “Normal Saline” as the treatment labels. Participant 1 had the randomization code: PHV1A (PHV denoted: paracetamol healthy volunteers, 1 denoted the participant number, and A denotes the first trial arm). As there were three trial arms, the second and third trial arms were respectively listed as “B” and “C” in each randomization code. All randomization codes were individually sealed in opaque envelopes. All study investigators were blinded to the trial fluid intervention. Independent hospital pharmacy staff provided the solutions in identical unmarked blinded vials. Treatment allocation was only revealed after data analysis was performed.

Statistical Methods

In order to determine a difference in MAP of 5 mmHg between the groups, given a baseline MAP of 90 mmHg, with an adjusted significance level of 0.025, a standard deviation of 3 mmHg, and a power of 0.9, 24 participants were recruited. Repeated measures analysis of variance modelling was performed by fitting the main effects for treatment (i.e. paracetamol, mannitol, NS) and time and an interaction between treatment and time to determine if the three treatments behaved differently over time. Within each variable, analysis was stratified by period

(pre-infusion, infusion, observation) so there were 3 sets of analysis for each variable. Because there were 3 groups, the overall p-value for a group effect simply answered the question "were these 3 groups significantly different from each other overall"; it did not inform us specifically where the differences were. For this assessment, we performed post-hoc analyses, looking for specific pairwise comparisons (paracetamol vs. mannitol, paracetamol vs. NS, mannitol vs. NS). To account for multiple comparisons, a reduced two-sided p-value of 0.01 was used to indicate statistical significance for post-hoc comparisons. Modelling was performed using the PROC Mixed procedure in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Twenty five participants were screened for eligibility. All participants were deemed eligible to participate in the trial after pre-study monitoring. One participant withdrew due to the time commitments required for the study. Withdrawal was prior to randomization. Twenty four healthy volunteers consented for this study and were randomized to receive three treatment arms in a randomly allocated order. All participants completed all interventions, and there were no breaches in the trial protocol. Fifty-eight-percent of the participants were male. The median (IQR) age and body mass index was 36.5 years (28-40.3 years) and 23.3 kg/m² (22.0-25.4 kg/m²), respectively. Baseline haemodynamic values together with the standard error of difference from the baseline (confidence intervals) are summarized in Table 1. There were no statistical differences in baseline demographic variables.

Primary ends points: MAP, SBP and DBP

The three groups were different when averaged across the infusion period and observation periods ($p < 0.001$). Changes in mean SBP, MAP and DBP during the infusions of paracetamol, mannitol and NS are graphically summarized in Figures 1-3. There were no decreases from baseline blood pressure with the infusions of mannitol and normal saline, but the infusion of paracetamol induced transient decreases in SBP, MAP, and DBP with a nadir at 15 minutes (end of infusion). In the paracetamol group compared to baseline values the mean SBP decreased by 0.5 mmHg (95% CI: -1.6 to 0.6), MAP decreased by 1.85 mmHg (95% CI: -2.6 to -1.1), and DBP decreased by 1.9 mmHg (95% CI: -2.6 to -1.2).

In the paracetamol group, the SBP, MAP, and DBP blood pressure variables remained significantly lower than the mannitol and saline groups ($p < 0.0001$) for the first 25 minutes. At the end of the 60 minute observation period, these changes were no longer present. These changes in blood pressure were not observed with mannitol, which showed a consistent increase in blood pressure during and after infusion with an peak effect at 60 minutes in SBP by 5.9 mmHg (95% CI: 4.3 to 7.5), MAP by 1.5 mmHg (95% CI: 0.8 to 3.1) and DBP by 0.8 mmHg (95% CI: -0.2 to 1.7). Compared to baseline values, infusion of NS resulted in negligible changes in blood pressure after 15 minutes: MAP 0.2 mmHg (95% CI: -0.9 to 0.6) and DBP 0.7 mmHg

(95% CI: -1.4 to 0.0), however produced the greatest increase in blood pressure at the end of the 60 minute observation period (MAP: +4.3 mmHg (95% CI: 3.2 to 5.5)).

Secondary ends points: SVRI, CI, SVI, HR

For all the secondary endpoints, there was statistical evidence to suggest that the three groups were different when averaged across the infusion and observation periods ($p < 0.001$). In the paracetamol group there was a transient reduction in SVRI decreasing by 88.3 mmHg/L/min/m² (95% CI: -147.4 to -29.2) immediately after the infusion ($p < 0.001$), which was similar to NS, which decreased by 124.0 mmHg/L/min/m² (95% CI: -64.9 to -183.1) (Figure 4). Approximately 25-30 minutes post infusion, the SVRI in the paracetamol group returned to pre-infusion values and then remained above baseline values until completion. SVRI for the paracetamol group peaked at 55 minutes after infusion with a total increase of 83.5 mmHg/L/min/m² (95% CI: 21.4 to 145.5). This post-infusion effect was significantly different from the mannitol and NS groups, with both groups increasing towards baseline 20 minutes after infusion.

In the mannitol group, compared to baseline values there was a transient increase in SVRI by 114.3 mmHg/L/min/m² (95% CI: 55.14 to 173.5), a finding not observed with the other two solutions. At the end of the study, SVRI for NS and mannitol were comparable (-31.5 mmHg/L/min/m² (95% CI: -93.5 to 30.5) vs -39.3 mmHg/L/min/m² (95% CI: -101.3 to 22.7)).

Post-hoc analysis of changes in SVRI between the 3 infusions over the duration of the study were primarily driven by paracetamol i.e. there was no statistical difference observed between mannitol and NS ($p=0.87$).

IV paracetamol induced a significant increase in CI during the infusion with a peak of increase of 0.09 L/min/m^2 from baseline (95% CI: 0.03 to 0.1), ($p<0.001$) at 15 minutes. This effect was maintained until the 20 minute time point. NS produced a similar increase in CI by 0.08 L/min/m^2 (95% CI: 0.0 to 0.1) during infusion, however CI continued to increase to a peak of 0.13 L/min/m^2 (95% CI: 0.0 to 0.2) at the 20 minute time point. Mannitol induced a transient decrease in CI during infusion with a nadir of -0.06 L/min/m^2 (95% CI: -0.1 to 0.0) at the 5 minute infusion time. Thereafter, CI returned to pre-infusion values by the end of the observation period. Post-hoc analysis of CI between the 3 infusions over the duration of the study showed that the changes in CI between the 3 infusions were primarily driven by paracetamol as evident by lack of a statistical difference observed between mannitol and NS ($p=0.13$).

During the infusion, the HR decreased significantly ($p<0.0001$) in all three groups and remained below baseline during the observation period. The decrease in HR was greatest in the mannitol group with an overall decrease at the end of the study in HR by 2.8 beats/min (95% CI: -3.9 to -1.6) at 30 minutes compared with paracetamol which decreased HR by 2.5 beats/min (95% CI: -3.5 to -1.2) at 35 minutes and NS which decreased HR by 1.4 beats/min (95% CI: -2.4 to -0.2) at

30 minutes. During the infusion of all three interventions, there were significant increases in SVI compared to pre-infusion values. SVI remained increased in all three groups throughout the observation period compared to pre-infusion values with a study end increase of 1.8 mL/m^2 (95% CI: 1.2 to 2.6) in the paracetamol group, 2.8 mL/m^2 (95% CI: 2.1 to 3.5) in the NS group and 2.9 mL/m^2 (95% CI: 2.1 to 3.6) in the mannitol group with paracetamol increasing by 1.9 mL/m^2 (95% CI: 1.2 to 2.6), NS increasing by 2.8 mL/m^2 (95% CI: 2.1 to 3.5) and mannitol increasing by 2.9 mL/m^2 (95% CI: 2.1 to 3.6).

Changes in Plasma osmolality

Plasma osmolality levels remained within the normal laboratory reference range (275-295 mOsm/kg) in all groups throughout the study. There were no statistical differences between the groups.

Reported Adverse Events

One participant in the saline group, and three in the mannitol group expressed a need to void urine after completion of the study. The volume of urine voided was not documented.

Discussion

Key study findings

We conducted a double-blinded, randomized, triple crossover study in healthy volunteers to compare intravenous paracetamol infusion (3.91 g mannitol + 1 g paracetamol/100 mL) with an equivalent administration of its excipient (mannitol) or placebo (NS). Our aim was to test the hypothesis of whether paracetamol itself is responsible for lowering arterial blood pressure. This healthy volunteer study provides plausible physiological data that IV paracetamol causes a transient decrease in BP immediately after infusion. These changes were not observed with mannitol or NS infusions suggesting that the adverse haemodynamic effects of paracetamol appear to be a function of the paracetamol itself, rather than that of its excipient - mannitol. Furthermore, the mechanism of this transient decrease in blood pressure appears to be secondary to a transient reduction in SVRI, and not due to a reduction in CI as previously reported.

Relationship to previous studies

Recently, in the context of critical illness, clinical studies have suggested that IV paracetamol may cause hypotension [1-8]. Most of these studies did not report on the possible mechanism for the hypotension observed [1, 3, 5-7]. In addition, all studies identified in our literature search were non-randomized, non-blinded, and uncontrolled, making it difficult to draw firm conclusions about this potential effect of paracetamol. One study reported anecdotal data [1] and others used small patient numbers [5, 6, 8]. Moreover, use of vasopressors could have also masked the magnitude of the adverse haemodynamic effects of paracetamol observed [2, 3, 5-7].

Recently, Krajcova et al. performed a non-blinded, non-randomized study on six intensive care patients who received 48 paracetamol and 35 control drug administrations [8]. These authors reported that IV paracetamol decreased CI. In contrast to these findings, we observed a small increase in CI after the infusion of paracetamol. Consistent with this increase in CI, we also observed an increase in SVI. The transient blood pressure changes observed in our study were associated with a reduction in SVRI. In the present study, we also investigated the effects of 3.91g of mannitol over a 15 minute infusion time. Sabharwal et al. studied 11 participants who were administered IV mannitol (1g/kg) over a 10 minute period and reported a decrease in blood pressure post infusion [16]. In contrast, we observed an increase in blood pressure during and post infusion of mannitol, albeit it at a much lower dose (1/20th). From the results our study, it is unlikely that the mannitol component present in the IV paracetamol formulation contributes to the haemodynamic effects we observed with the paracetamol infusion.

Study implications

The clinical implication of our findings in this healthy volunteer study is that IV paracetamol transiently lowers arterial blood pressure. The effects of paracetamol on haemodynamics could be considered clinically insignificant, however, these haemodynamics derangements may have different intensities and durations in patients who are already haemodynamically compromised. The mechanism of paracetamol-induced hypotension has previously been reported to be secondary to a reduction in CI in a non-randomized non-blinded study. In contrast, we observed

that the decrease in blood pressure was due to a reduction in SVRI, and not CI. Of particular importance was the increase in SVRI in the mannitol observed shortly after its infusion. Taking into consideration the mannitol content of the IV paracetamol formulation used in our study, the true value of the observed reduction in SVRI may have been further masked by the effects of mannitol. Further studies may be required to examine these effects in non-mannitol containing IV paracetamol formulations. The observed reduction in SVRI may have clinically important implications when considering the administration of IV paracetamol to patients with low SVR states e.g. septic shock or post-operative inflammatory vasodilatation.

Strengths and limitations

This study has several methodological strengths. It is blinded and randomized, thus minimizing selection and assessment bias and increasing internal validity. It is a triple crossover study, which reduces the influence of confounding covariates. The concealment of the intervention further decreased selection bias. Comprehensive electronic data collection using continuous beat-to-beat measurements of haemodynamic variables of the Edwards Lifesciences Nexfin™ enabled detailed quantitative comparisons. Furthermore, SBP, DBP, MAP and HR were all objective variables not amenable to ascertainment bias or manipulation, and our findings were further strengthened by measurements of derived physiological haemodynamic data such as CI and SVRI. Finally, to date this is the first study to comprehensively compare IV paracetamol (1 g paracetamol + 3.91 g mannitol/100 mL), its excipient - mannitol (3.91 g mannitol/100 mL) and

placebo (NS) over a 60 minute period.

There are also several limitations to our study. First, the changes in blood pressure observed were small and could be considered clinically insignificant. Similarly, the increase in SVRI seen with mannitol at 15 minutes should also be interpreted with caution. Given that SVRI has a wide normal range between 1970-2396 mmHg/L/min/m², changes observed in SVRI could also be considered to be within normal limits and not of clinical importance. Secondly, the trial was small and only powered to demonstrate composite changes in blood pressure, and not changes in SVRI or CI, which are derived variables. Whilst the use of the Lifesciences Nexfin™ invasive haemodynamic is well validated in many clinical studies, and validated against both the sphygmomanometer and arterial line, measurement of central venous pressure via a central venous catheter would have been useful in identifying the effects of the paracetamol on preload and in more accurately calculating SVRI. The use of a central venous catheter and other invasive haemodynamic monitoring tools, (e.g. arterial line, pulmonary artery catheter) were considered too invasive in a healthy volunteer population. Although we did not use invasive techniques to measure arterial blood pressure and cardiac output, the accuracy of the Nexfin™ cardiac output technology has been validated against pulmonary thermodilution [17], transpulmonary thermodilution [18], transoesophageal and transthoracic echocardiography [19, 20], and inert gas rebreathing [21]. Percentage errors range from 23% to 39%, comparable to more invasive methods [17, 21]. Larger errors have been reported, but these are in the setting of critically ill patients where compromised flow to the finger may affect Nexfin™ performance [22]. This is

clearly not applicable in a healthy volunteer setting making it physiologically plausible that the NexfinTM technology used was able to reliably track changes in CI, a finding supported by other studies [17, 18, 23]. Use of transthoracic echocardiography would have allowed valuable non-invasive and focused estimations of cardiac function and fluid responsiveness. However, its continuous use over the entire duration of each experiment was not pragmatic, and lack of availability of a dedicated TTE machine and a skilful operator for all experiments unfortunately precluded its use. Finally, whilst the carrier solution in IV paracetamol is sterile water, we used NS as the placebo solution as 100 mL infusion of either solution over a 15 minute period would have little, if any effect, on haemodynamic differences.

In summary, in a double-blinded, randomized, triple crossover healthy volunteer study, we found evidence that IV paracetamol caused a transient decrease in BP after infusion when compared with its excipient (mannitol) and placebo (NS). The reduction in blood pressure was most noticeable at 15 minutes, returning to baseline values within 30 minutes. These findings appear to be a function of the paracetamol itself, rather than that of its excipient - mannitol. The primary physiological mechanism of these haemodynamic changes was transient systemic vasodilatation, rather than a reduction in CI. This study provides plausible physiological data in a healthy volunteer setting, which supports the recently reported adverse haemodynamic effects of IV paracetamol in the critical care setting and suggests the need for similar double-blinded, randomized controlled trials in patients.

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Declaration of competing interests

All authors have completed the Unified Competing Interest form at

http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author)

and declare: no support from any organisation for the submitted work for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Meetings at which this work has been presented

This trial was presented at Euroanesthesia, The European Anesthesiology Congress Conference 2015, 30th May-2nd June 2015, Berlin, Germany.

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Figure and Table Legends

Figure 1. Changes in systolic blood pressure (SBP) including standard error bars from baseline pre-infusion (Pre), during a 15 minute infusion period (Inf), and 60 minute post-infusion (Obs) of paracetamol, mannitol and NS. (Repeated measures ANOVA, $p < 0.001$)

Figure 2. Changes in mean arterial pressure (MAP) including standard error bars from baseline pre-infusion (Pre), during a 15 minute infusion period (Inf), and 60 minute post-infusion (Obs) of paracetamol, mannitol and NS. (Repeated measures ANOVA, $p < 0.001$)

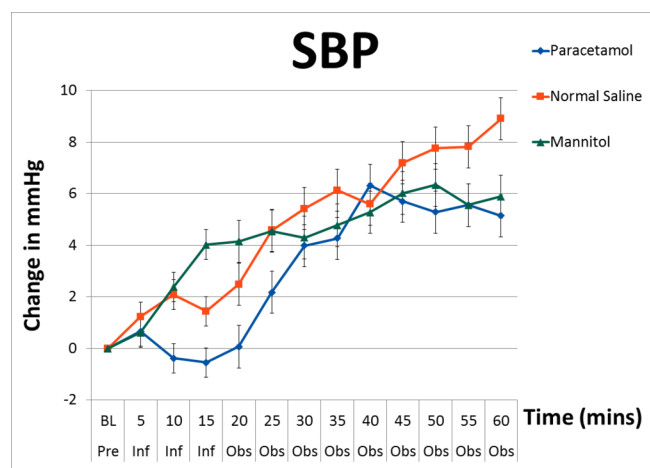
Figure 3. Changes in diastolic blood pressure (DBP) including standard error bars from baseline pre-infusion (Pre), during a 15 minute infusion period (Inf), and 60 minute post-infusion (Obs) of paracetamol, mannitol and NS. (Repeated measures ANOVA $p < 0.001$)

Figure 4. Changes in systemic vascular resistance index (SVRI) including standard error bars from baseline pre-infusion (Pre), during a 15 minute infusion period (Inf), and 60 minute post-infusion (Obs) of paracetamol, mannitol and NS. (Repeated measures ANOVA, $p < 0.001$)

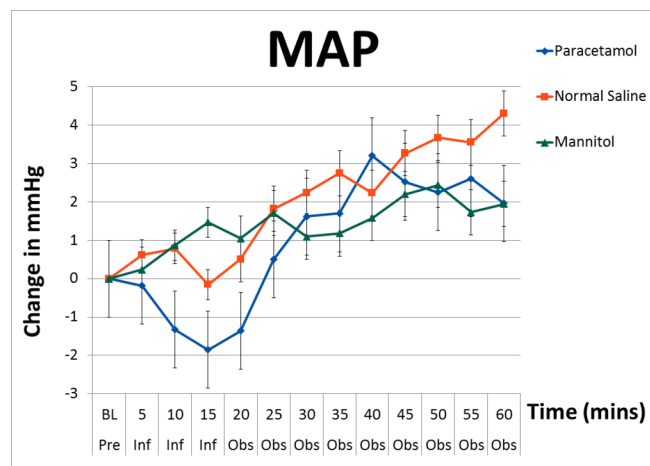
Figure 5. Changes in cardiac index (CI) including standard error bars from baseline pre-infusion (Pre), during a 15 minute infusion period (Inf), and 60 minute post-infusion (Obs) of paracetamol, mannitol and NS. (Repeated measures ANOVA, $p < 0.001$)

Table 1. Baseline haemodynamic demographics. Shown as absolute values $\pm$ standard error of difference between trial arms.

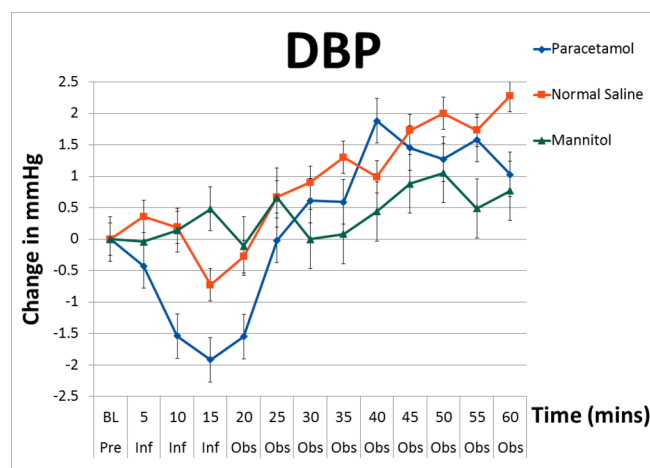
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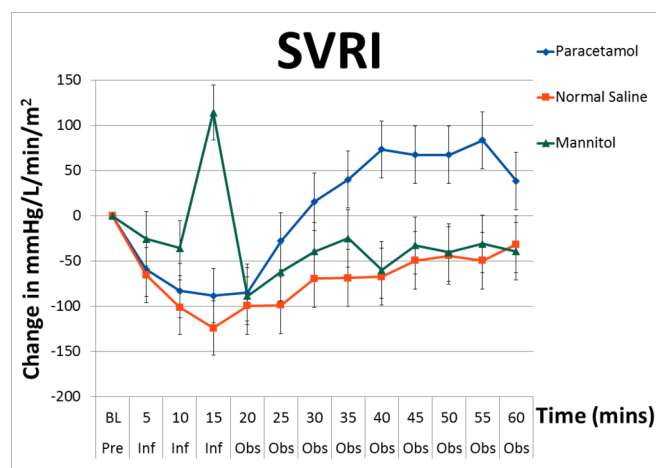
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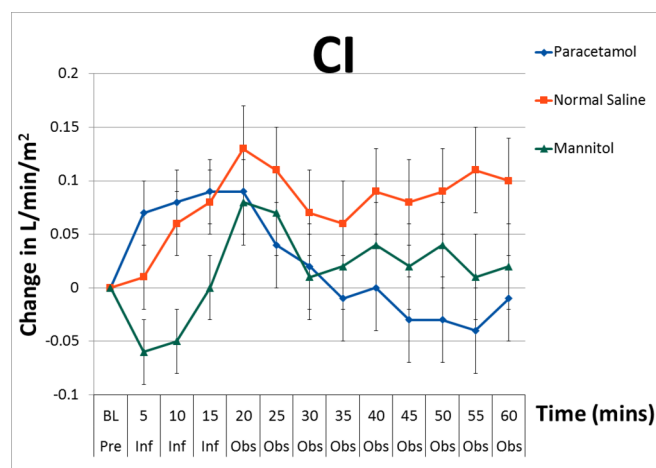
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Baseline Variable	Treatment	Mean (SE)
SBP (mmHg)	Paracetamol	121.1 (1.7)
	Saline	123.6 (1.7)
	Mannitol	122.4 (1.7)
MAP (mmHg)	Paracetamol	91.6 (1.3)
	Saline	94.0 (1.3)
	Mannitol	92.7 (1.3)
DBP (mmHg)	Paracetamol	72.2 (0.97)
	Saline	74.4 (0.97)
	Mannitol	73.2 (0.97)
SVRI (mmHg/L/min/m ²)	Paracetamol	2285 (100.5)
	Saline	2450 (100.4)
	Mannitol	2342 (100.5)
CI (L/min/m ²)	Paracetamol	3.4 (0.17)
	Saline	3.3 (0.17)
	Mannitol	3.4 (0.17)
HR (b/min)	Paracetamol	64.4 (2.2)
	Saline	69 (2.2)
	Mannitol	65.5 (2.2)
SVI (ml/m ²)	Paracetamol	52.5 (1.1)
	Saline	51.3 (1.1)
	Mannitol	52.1 (1.1)