IN BRIEF

- This study has shown the benefits of soluble aspirin (900 mg) over solid paracetamol (1,000 mg) in the control of postoperative pain after third molar extractions.
- The aspirin preparation provided an earlier onset of pain relief when compared with paracetamol.
- Most patients in the study did require additional analgesia in the early postoperative period, but the time to remedication was significantly longer in soluble aspirin group when compared with the placebo.
- Adverse events due to the medication were few and showed no differences between treatment groups.
- Soluble aspirin 900 mg appears to be a more useful analgesic than paracetamol in the control of postoperative pain after third molar surgery

# An investigation into the comparative efficacy of soluble aspirin and solid paracetamol in postoperative pain after third molar surgery

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**Objective** To compare the efficacy of soluble aspirin 900 mg and paracetamol 1,000 mg in patients with postoperative pain after third molar surgery.

**Design** A randomised, placebo controlled, double-blind study.

**Setting** Day stay units of Oral and Maxillofacial Surgery at Cardiff Dental Hospital and Hexham General Hospital, Northumberland.

**Subjects and methods** One hundred and sixty-seven (104 female) patients who required the removal of their impacted third molars under general anaesthesia.

**Intervention** In the early postoperative period, patients were medicated with either a single dose of soluble aspirin 900 mg, solid paracetamol 1,000 mg or placebo.

**Main outcome measures** Pain intensity was measured on 100 mm visual analogue scales at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120 and 240 minutes after dosing. Other efficacy variables evaluated included time to rescue medication and an overall assessment of the study medication efficacy by the patient on completion of the study.

**Results** One hundred and sixty-seven patients consented to take part in the study, but only 153 were medicated. Of the 14 patients not treated, 10 failed to develop sufficient pain to enter the study, two withdrew consent, one had an adverse reaction to the general anaesthetic and one was a protocol violator. Over the four hour investigation period, patients treated with soluble aspirin reported significantly less pain when compared with those treated with paracetamol (mean difference in $AUC_{0-240}$ = -2001, 95% CI −3893 to −109, p=0.038) and placebo (mean difference in $AUC_{0-240}$ = -3470, 95% CI −5719 to −1221, p=0.003). Similarly, at 20 and 30 minutes after dosing, patients in the soluble aspirin group were reporting significantly less pain than those in the paracetamol treatment group (mean difference in pain intensity: at 20 minutes −7.9, 95% CI −15.3 to −0.6, p=0.035; at 30 minutes −10.6, 95% CI −18.6 to −2.6, p=0.010). There were no significant differences between treatment groups with respect to the number of patients requiring rescue medication, however the time to dosing was significantly longer for those taking soluble aspirin when compared with placebo (hazard ratio 2.34, 95% CI 1.41 to 3.88, p<0.001).

**Conclusion** The findings from this study showed that soluble aspirin 900 mg provides significant and more rapid analgesia than paracetamol 1,000 mg in the early postoperative period after third molar surgery.

## INTRODUCTION

Both aspirin (acetylsalicylic acid) and paracetamol (acetaminophen) are widely available analgesics. The drugs are used extensively in dentistry, either self-prescribed by the patient or recommended by the dental surgeon. Despite such use, there have been few comparative studies on these analgesics and the studies published seem to suggest that the drugs are equi-analgesic.[1] More recent evidence suggests that many factors appear to influence the efficacy of aspirin in postoperative dental pain. These include formulation, dose and plasma concentration of acetylsalicylate.[2-5] The latter appears to be determined by plasma aspirin esterase activity. By contrast, there is limited information on the efficacy of paracetamol in postoperative dental pain.

Historically, there have been many studies comparing the efficacy of a whole range of analgesics which have used aspirin as the standard treatment (positive control). In such studies, the formulation chosen has invariably been a solid format of the drug. This has led to the impression that aspirin is relatively weak and slow acting. Previous studies[3,4] have shown that soluble aspirin provides a greater onset of action and is overall more effective than solid aspirin. However, up to the present time, there has been no study comparing the efficacy of soluble aspirin with solid paracetamol. The present study was designed to investigate whether the superiority of soluble aspirin over solid aspirin would be reproduced when compared with solid paracetamol. The doses chosen for each

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preparation used in this study is the maximum recommended when purchased as over the counter (OTC) medications.

Removal of impacted third molars remains a common dental surgical procedure that results in a significant level of postoperative pain.[6] Pain is usually of short duration and reaches its maximum intensity in the early postoperative period.[7] It is during this time period that analgesics are frequently prescribed. The nature of the pain and its duration make the third molar pain model useful for evaluation of analgesic efficacy.

The overall aim of the present study was to directly compare the efficacy of soluble aspirin with that of solid paracetamol tablets in patients with postoperative pain after third molar surgery. A placebo group was also used to act as a negative control. Within this overall remit, the primary aim of the study was to compare the onset of efficacy between the two preparations.

## MATERIAL AND METHODS

Adult patients who required the removal of at least one impacted lower third molar were invited to participate in the study. Patients were enrolled from two centres (Cardiff and Hexham). Informed written consent was obtained from each patient prior to their entry into the study, which had received ethical approval from the appropriate local Health Authority Ethical Committees. Patients enrolled into the study were fit and healthy and complied with the criteria of the American Society of Anaesthesiologists, category one, or, at the discretion of the dental surgeon, category two. All patients attended a screening clinic prior to their participation in the study. The pre-screening was held up to a maximum of three weeks before surgery. Patients were asked to abstain from taking any analgesics for 24 hours prior to their third molar extractions.

Patients underwent the removal of their impacted third molars under general anaesthesia. The anaesthetic regimen was according to routine clinical practice at the dental centre and included induction with intravenous propofol. Muscle relaxation was achieved with vecuronium, atracurium, pancurium, mivacurium or suxamethonium. Anaesthesia was maintained with nitrous oxide, oxygen and either isoflurane, enflurane or sevoflurane. Perioperative analgesia was provided by fentanyl or alfentanyl.

Impacted third molars were removed following a standard technique. Bone removal was carried out with a drill under saline spray. The operating time (from first incision to completion of last suture) was recorded for each patient. On completion of the surgical procedure, time was allowed for the patients to recover fully from the effects of the anaesthetic. They were then returned to the ward where they were monitored by the study nurse and their pain intensity assessed on 100 mm visual analogue scales (VAS). The boundaries of the scale were marked 'no pain' and 'worst pain imaginable'. When patients' pain intensity reached a level in excess of 30 mm on the VAS, they were randomised to study medication. Patients whose pain intensity did not reach the required level or who did not request analgesia within 1½ hours post-operatively were withdrawn from the study. Each eligible patient was randomly allocated to one of the following treatment groups: soluble aspirin (Disprin®) 900 mg, solid paracetamol tablets BP 1,000 mg or placebo. In order to double-blind the study, a double-dummy technique was used. Each patient assigned to receive active soluble aspirin or active solid paracetamol also received a placebo for the alternative treatment and placebo patients received a placebo for both formulations. Soluble aspirin and the aspirin placebo were presented as an orange drink. Paracetamol active and placebo were given as tablets. Patients were randomised to treatment groups in the ratio of 2 aspirin:2 paracetamol:1 placebo. The randomisation was stratified for gender. A randomisation block size of five was used to ensure balance between the treatment groups.

### Pain assessment

The following measures were used to evaluate efficacy:

a) Pain intensity measures were recorded immediately pre-dose (0 minutes) and at 5, 10, 15, 20, 30, 45, 60, 90, 120 and 240 minutes after dosing. Onset of analgesia was primarily assessed by pain intensity measures at 10, 15, 20 and 30 minutes.

b) Pain intensity over the four hour investigation period.
The serial VAS measures of the four hour investigation period were compiled into a graph of pain (mm) versus time (minutes). The area under the graph (AUC) was calculated using the trapezoidal method and denoted as $AUC_{240}$. Such a measure gives an overall assessment of each patient's pain experience throughout the four hour investigation period.[8]

c) Use of rescue medication.
In the event of poor pain control, patients were allowed access to alternative analgesia (ibuprofen, 400 mg). Patients were encouraged not to request re-medication in the first hour post-dosing in order to give the study medication time to work. For those taking additional analgesics, the time was recorded and their last pre-rescue medication intensity score was extrapolated over the remaining time points.[9]

d) Overall evaluation.
At the end of the four hour investigation period (or prior to taking rescue medication), the study nurses and the patients were asked to provide an overall evaluation of the efficacy of the study medication. The categories were 'very good', 'good', 'satisfactory', 'poor' and 'very poor'.

Throughout the investigation period, a study nurse was responsible for monitoring the patients and recording any adverse events.

### Statistical methods

A previous study in postoperative pain after removal of impacted third molars[4] suggested that mean VAS differences between soluble aspirin and placebo, and soluble aspirin and solid paracetamol of 26 mm and 14 mm respectively might be anticipated at 20 minutes post treatment. Using a randomisation of 2 soluble aspirin: 2 paracetamol: 1 placebo, a total sample size of 150 patients had at least 80% power to detect this difference.

The VAS pain intensity measurements at 10, 15, 20 and 30 minutes after dosing, and $AUC_{240}$ were compared between treatment groups using an analysis of covariance, using centre, gender, baseline pain intensity, operation duration and number of

**Table 1 Demographic details of patients who were medicated for the study. Where appropriate, results are expressed as mean (SD)**

| Variable | | Soluble aspirin 900 mg | Solid paracetamol 1,000 mg | Placebo |
|---|---|---|---|---|
| Number of patients | | 59 | 62 | 32 |
| Gender ratio M:F | | 19:40 | 19:43 | 11:21 |
| Age (years) | | 25.6 (5.6) | 25.0 (5.3) | 25.1 (4.7) |
| Weight (kg) | | 70.2 (16) | 71.9 (14.5) | 74.3 (14.9) |
| Mean operating time (mins) | | 17.3 (10.1) | 16.5 (10.1) | 13.0 (13.0) |
| Number of molars removed | 1 | 3 (5%) | 2 (3%) | 3 (9%) |
| [# patients (%)] | 2 | 15 (25%) | 14 (23%) | 5 (16%) |
| | 3 | 11 (19%) | 12 (19%) | 9 (28%) |
| | 4 | 30 (51%) | 34 (55%) | 15 (47%) |
| Mean baseline pain score on 100 mm VAS | | 57.4 (17.6) | 50.6 (14.2) | 54.1 (14.4) |

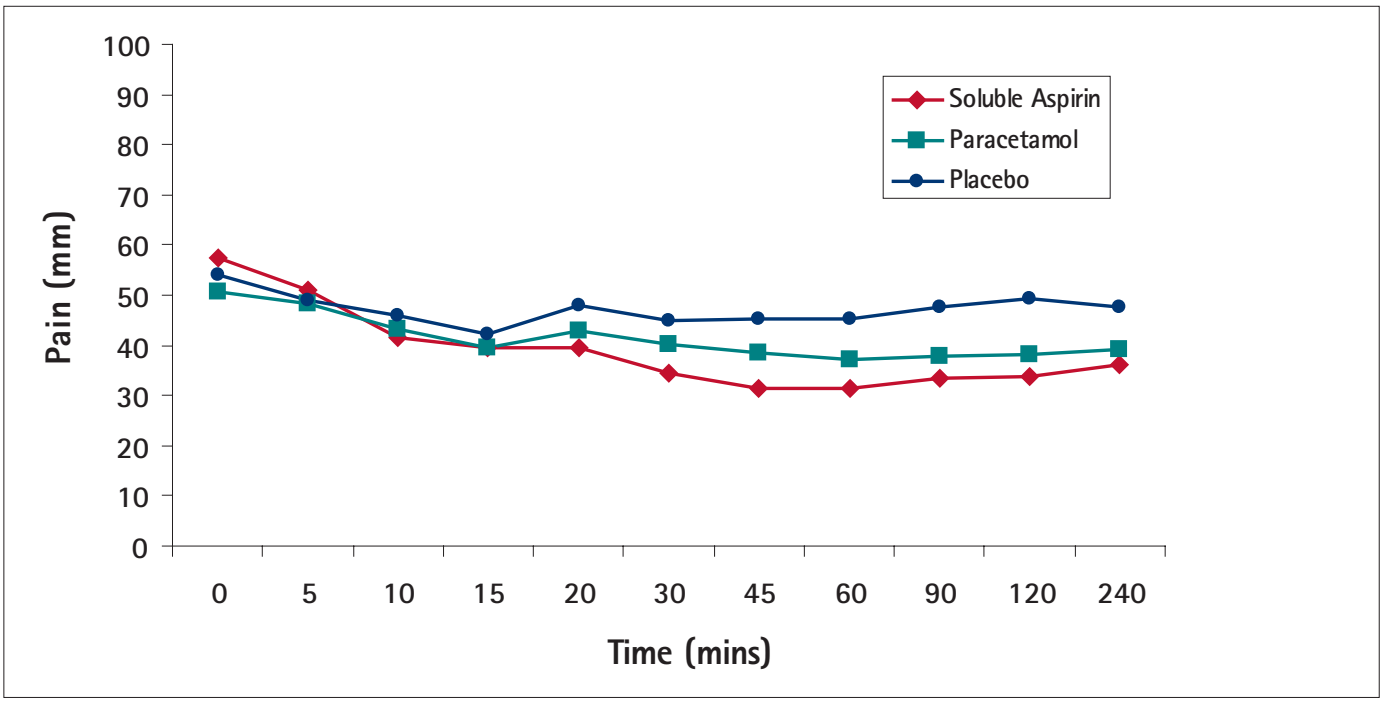


**Figure 1 Graph to show mean pain scores (mm) versus time (mins) for patients after treatment with placebo, solid paracetamol 1,000 mg and soluble aspirin 900 mg.**

molars removed as covariates. Use of rescue medication and the study nurses' and patients' overall impression of their medication were analysed using binomial logistic regression with a 'positive' outcome defined as a response of 'very good' or 'good'. Time to administration of rescue medication was compared between treatment groups using Cox's proportional hazard model. Comparisons were performed for soluble aspirin versus solid paracetamol and soluble aspirin versus placebo.

## RESULTS

One hundred and sixty seven patients consented to take part in the study and 153 were medicated. Of these, 29 were medicated in Hexham and the remainder in Cardiff. Of the 14 patients not treated, 10 failed to develop sufficient pain to enter the study, two withdrew consent, one had an adverse reaction to the anaesthesia and one was a protocol violator. Demographic details of the patients are shown in Table 1. The three groups were balanced for demographic variables.

The primary aim of the study was to compare the rate of onset of analgesia and the 20-minute time was considered to be appropriate for such an assessment. Pain scores as recorded on the VAS at each time point are illustrated in Figure 1 and Tables 2a and 2b. VAS scores decreased in all treatment groups during the first 15 minutes post dosing (Figure 1). At 20 minutes post dosing, patients in the sol-

**Table 2a Summary of efficacy parameters recorded during the investigation period: pain scores.**

| | | | | Between treatment comparisons | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Soluble aspirin 900 mg | Solid paracetamol 1,000 mg | Placebo | Soluble aspirin vs placebo | | | Soluble aspirin vs solid paracetamol | | |
| | | | | Mean difference | (95% CI) | p-value | Mean difference | (95% CI) | p-value |
| Pain score (in mm) 10 mins after dosing * | 41.2 (2.8) | 48.2 (2.9) | 47.4 (3.3) | -6.1 | (-13.3 to 1.0) | 0.092 | -7.0 | (-13.0 to –0.9) | 0.024 |
| Pain score (in mm) 15 mins after dosing * | 40.7 (3.2) | 45.8 (3.3) | 44.5 (3.8) | -3.9 | (-12.0 to 4.3) | 0.350 | -5.1 | (-12.0 to 1.8) | 0.143 |
| Pain score (in mm) 20 mins after dosing * | 40.2 (3.4) | 48.1 (3.5) | 50.0 (4.0) | -9.8 | (-18.6 to –1.1) | 0.028 | -7.9 | (-15.3 to –0.6) | 0.035 |
| Pain score (in mm) 30 mins after dosing * | 35.6 (3.7) | 46.2 (3.8) | 47.6 (4.4) | -12.0 | (-21.6 to –2.5) | 0.014 | -10.6 | (-18.6 to –2.6) | 0.010 |
| Overall pain - $AUC_{240}$ (mm/mins) * | 8,001 (871) | 10,002 (898) | 11,471 (1035) | -3470 | (-5,719 to –1,221) | 0.003 | -2,001 | (-3,893 to –109) | 0.038* |

*data presented are adjusted (least squares) mean (standard error of the mean)

**Table 2b Summary of efficacy parameters recorded during the investigation period: use of escape medication**

| | | | | Between treatment comparisons | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Soluble aspirin 900 mg | Solid paracetamol 1,000 mg | Placebo | Soluble aspirin vs placebo | | | Soluble aspirin vs solid paracetamol | | |
| | | | | Odds (hazard) ratio | (95% CI) | p-value | Odds (hazard) ratio | (95% CI) | p-value |
| Number of patients taking escape analgesics | 48 (81%) | 46 (74%) | 29 (91%) | 0.172 | (0.020 to 1.052) | 0.078 | 1.485 | (0.455 to 5.197) | 0.518 |
| Time (minutes) to remedication** | 115 (63 - 165) | 94 (47 - ++) | 64 (42 – 117) | 2.34 | (1.41 to 3.88) | <0.001 | 1.30 | (0.84 to 2.03) | 0.236 |

** data presented are median (Inter Quartile Range)
++ Upper quartile cannot be estimated

uble aspirin group reported significantly less pain than those treated with solid paracetamol (p=0.035) or placebo (p=0.028). Similarly pain intensity was significantly less at 10 and 30 minutes post dosing for patients treated with soluble aspirin when compared with solid paracetamol (p=0.024 and 0.010 respectively). Pain intensity was also significantly less for patients treated with soluble aspirin when compared with placebo at 30 minutes post dosing (p=0.014) but was not significant at 10 minutes post-dosing (p=0.092). By contrast to these findings, at 15 minutes after dosing, pain scores were not significantly different between soluble aspirin and placebo (p=0.350) or between soluble aspirin and solid paracetamol (p=0.143). Overall pain scores, as assessed by the $AUC_{240}$, were significantly lower in the soluble aspirin group when compared with solid paracetamol (p=0.038) and placebo (p=0.003). There was no significant centre difference for any of the pain intensity variables.

The use of rescue medication and time to requesting such medication is also shown in Table 2b. There was no significant difference between soluble aspirin and solid paracetamol or placebo with respect to the number of patients requiring rescue medication during the four hour investigation period (p>0.05). However the time to administration of rescue medication was significantly longer for those patients taking soluble aspirin when compared with placebo (p<0.001). There was no significant difference in time to rescue medication between the soluble aspirin treated patients and those treated with solid paracetamol (p=0.236). The time to administration of rescue medication did show a significant centre effect, with those patients enrolled in Cardiff requiring rescue analgesia at an earlier time point than those in Hexham (p<0.001).

The study nurses' and patients' overall assessment of the efficacy of the medication is shown in Tables 3a and 3b. There was no significant difference between soluble aspirin and solid paracetamol (p=0.285) with respect to the percentage of 'positive' outcomes assessed by the patients, however soluble aspirin was favoured in comparison with placebo (p=0.010). Results were similar for the study nurses' assessment (p=0.387, p=0.024).

Adverse events were reported by 41% of patients with a higher overall incidence in the active treatment groups (Table 4). Many of these events were related to the procedure. The most common adverse events were in the central and peripheral nervous system (primarily dizziness) and the gastro-intestinal system (primarily nausea). The incidence of dizziness was similar in the soluble aspirin and placebo groups (14% and 13% respectively) and was greater than in the solid paracetamol group (6%). The incidence of nausea was comparable in the soluble aspirin and solid paracetamol groups (15% and 16% respectively) and was greater than that in the placebo group (6%). Gingival bleeding (the only adverse event recorded under 'haemostasis') had a slightly lower incidence in the soluble aspirin group (8%) than in the solid paracetamol group (13%) and was only slightly higher than that reported in the placebo group (3%). This finding is contrary to any expectations that aspirin might exacerbate post-operative bleeding.

## DISCUSSION

The present study has shown that soluble aspirin 900 mg is an effective analgesic in the control of postoperative pain after the removal of impacted third molars, confirming the evidence from previous studies.[3,4] In addition, soluble aspirin provided better pain control than solid paracetamol 1,000 mg. This superior efficacy is reflected in the overall pain score (Table 2a and Figure 1) and also in the pain scores reported during the first 30 minutes post dosing. The data suggest that soluble aspirin is providing a more rapid reduction in pain in the early postoperative period when compared with solid paracetamol. If the pain scores are examined in terms of percentage reduction when compared with baseline, the results show that soluble aspirin is twice as effective as solid paracetamol (at 20 and 30 minutes the percentage reduction for soluble aspirin is 31.0% and 40.6% respectively whilst the figures for solid paracetamol are 14.2% and 20.4%). From the perspective of patient management, a rapid reduction in pain is an important requisite of any analgesic formulation.[10] The exception to this pattern is the pain scores at 15 minutes post dosing. At this time point, pain intensity scores after soluble aspirin are not significantly different from either placebo or solid paracetamol – the reason for this finding is unclear.

Previous comparative efficacy studies between aspirin and paracetamol in postoperative dental pain have revealed somewhat equivocal results.[1,11,12] The consensus view[1] is that both aspirin and paracetamol are both equi-analgesic and equipotent. The studies use a solid tablet formulation of aspirin at a dose of 650 mg. Studies using similar methodology have shown that the efficacy of aspirin in postoperative dental pain is related to dose and formulation.[3,4] The use of a soluble formulation and the 900 mg dose may explain the superior efficacy of aspirin in this study.

**Table 3a Distribution of scores from patients' global assessment of the medication (number (%))**

| Score | Soluble aspirin 900 mg | Solid paracetamol 1,000 mg | Placebo | Soluble aspirin vs placebo | | | Soluble aspirin vs solid paracetamol | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Odds Ratio | (95% CI) | p-value | Odds Ratio | (95% CI) | p-value |
| Positive outcome * | 34 (58%) | 33 (53%) | 10 (31%) | 3.591 | (1.402 to 9.828) | 0.010 | 1.530 | (0.706 to 3.380) | 0.285 |
| Very good | 15 (25%) | 12 (19%) | 3 (9%) | | | | | | |
| Good | 19 (32%) | 21 (34%) | 7 (22%) | | | | | | |
| Satisfactory | 15 (25%) | 12 (19%) | 10 (31%) | | | | | | |
| Poor | 8 (14%) | 15 (24%) | 9 (28%) | | | | | | |
| Very poor | 2 (3%) | 2 (3%) | 3 (9%) | | | | | | |
| Total | 59 | 62 | 32 | | | | | | |

* positive outcome = response of 'very good' or 'good'

**Table 3b Distribution of scores from study nurses' global assessment of the medication (number (%))**

| Score | Soluble aspirin 900 mg | Solid paracetamol 1,000 mg | Placebo | Soluble aspirin vs placebo | | | Soluble aspirin vs solid paracetamol | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Odds Ratio | (95% CI) | p-value | Odds Ratio | (95% CI) | p-value |
| Positive outcome * | 32 (54%) | 32 (52%) | 10 (31%) | 2.974 | (1.179 to 7.951) | 0.024 | 1.403 | (0.655 to 3.054) | 0.387 |
| Very good | 15 (25%) | 11 (18%) | 3 (9%) | | | | | | |
| Good | 17 (29%) | 21 (34%) | 7 (22%) | | | | | | |
| Satisfactory | 17 (29%) | 14 (23%) | 12 (38%) | | | | | | |
| Poor | 8 (14%) | 14 (23%) | 7 (22%) | | | | | | |
| Very poor | 2 (3%) | 2 (3%) | 3 (9%) | | | | | | |
| Total | 59 | 62 | 32 | | | | | | |

* positive outcome = response of 'very good' or 'good'

**Table 4 Incidence and distribution of adverse events for each treatment group**

| Percentage of patients reporting events (number of events) | | | | |
|---|---|---|---|---|
| Body system | Soluble aspirin (n=59) | Solid paracetamol (n=62) | Placebo (n=32) | Total (n=153) |
| CNS | 20 (14) | 8 (5) | 19 (6) | 15 (25) |
| GI | 17 (12) | 16 (12) | 6 (2) | 14 (26) |
| Body as a whole | 7 (4) | 13 (8) | 6 (3) | 9 (15) |
| Haemostasis | 8 (7) | 13 (8) | 3 (1) | 9 (16) |
| Respiratory | 7 (4) | 3 (2) | 0 (0) | 4 (6) |
| Psychiatric | 2 (1) | 0 (0) | 3 (1) | 1 (2) |
| Hearing/vestibular | 0 (0) | 2 (1) | 0 (0) | 1 (1) |
| Skin/appendages | 2 (1) | 0 (0) | 0 (0) | 1 (1) |
| Vision | 2 (1) | 0 (0) | 0 (0) | 1 (1) |
| Total | 51 (44) | 39 (36) | 28 (13) | 41 (93) |

The primary aim of this investigation was to compare both analgesics with respect to onset of action. Early time points were chosen for this comparison as they represent a suitable period from dosing when patients would expect to experience meaningful pain relief. Soluble aspirin was significantly superior to both placebo and solid paracetamol at both 20 and 30 minutes post dosing and there were indications of superiority as early as at 10 minutes. In part, this may be due to the rapid absorption of soluble aspirin and the subsequent peak concentrations of acetylsalicylate (Tmax) that occurs at these time points. It has been previously shown that plasma concentrations of acetylsalicylate are also important determinants of aspirin's efficacy in postoperative dental pain.[2] By contrast, the absorption of solid paracetamol tablets is slow with a Tmax of 60 minutes.[13] Thus differences in pharmacokinetics may account for the differences in onset of analgesia observed in the present study.

It is now well established that aspirin exerts both analgesic and anti-inflammatory action by inhibiting prostaglandin synthesis.[14] Aspirin irreversibly inhibits both cyclo-oxygenase 1 and 2 (Cox-1 and Cox-2) by acetylating serine 530, thus preventing the binding of arachidonic acid to the active sites of the enzyme. The pharmacodynamics of paracetamol are uncertain, and by comparison with aspirin, the drug exhibits weak anti-inflammatory action. This lack of a pronounced anti-inflammatory effect may also explain the weaker efficacy of this drug in postoperative dental pain.

We can conclude from this study that a single dose of soluble aspirin 900 mg provides significant and more rapid analgesia than solid paracetamol 1,000 mg in the early postoperative period after third molar surgery. This study confirms the value of soluble aspirin in the management of pain after dental surgical procedures.

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