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Use of Paracetamol and Ibuprofen in Combination for Pain Relief in Children after Oral Surgery

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Abstract

The aim of this study was to determine the use of paracetamol and ibuprofen in combination for pain relief in children after oral surgery. Children under 10 years old having one or more wisdom teeth removed under general or local anaesthesia were instructed to take two tablets before the operation then, every 4 h for up to 48 h, two tablets of a combination of acetaminophen 250 mg and ibuprofen 150 mg per tablet and acetaminophen 250 mg per tablet alone and ibuprofen 150 mg per tablet alone. The primary outcome measure was the area under the curve of the 100 mm visual analogue scale of pain measurements taken for up to 36 h after surgery, divided by time, at rest and in activity. The result showed that although all four secondary endpoints favoured the combination treatment, only the global pain rating reached statistical significance. More participants experienced 'nil' or 'mild' pain with the combination (68.4%) than with either other group; this difference was significant for acetaminophen (37.5%; P=0.008), but not for ibuprofen (54.3%; P=0.263). The use of any rescue medication also favoured the combination treatment, but this did not reach statistical significance. In conclusion, we demonstrated that patients using the combination of acetaminophen and ibuprofen experienced less pain during the first 48 h after oral surgery than those using the same daily dosage of either agent alone and we think the difference was clinically relevant.

Keywords: Paracetamol; Ibuprofen; Pain relief; Surgery; Children

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) have fewer regulatory restrictions (Cousins *et al.,* 2004), but they too have important adverse effects which are more likely at higher doses or with longer courses (Merry, 1995).

Acetaminophen is often used with a non-steroidal anti-inflammatory drug for acute pain (Altman, 2004). These drugs have had to be given separately, typically at different time intervals (Mehlisch, 2002). This drug is also used to treat mild to moderate pain from headaches, menstrual periods, toothaches, backaches, osteoarthritis, aches and pains from colds and flu, and to reduce fever (Anderson & Cranswick, 2005). Acetaminophen, also known as paracetamol, is commonly used for its analgesic and antipyretic effects (Barden *et al.,* 2004). Its therapeutic effects are similar to salicylates, but it lacks anti-inflammatory, antiplatelet and gastric ulcerative effects. Ibuprofen is a medication in the none-steroidal anti-inflammatory drug (NSAID) class that is used for treating pain, fever (Rainsford, 1999), and inflammation (Cooper *et al.,* 1989; Desmeules *et al.,* 2003). This includes painful menstrual periods, migraines and rheumatoid arthritis. It may also be used to close a patent ductus arteriosus in a premature baby (Viitanen *et al.,* 2003). It can be taken by mouth or intravenously (Menhinick *et al.,* 2003). It typically begins working within an hour. Common side effects include heartburn and a rash (Prescott, 2001). Compared to other NSAIDs, it may have fewer side effects such as gastrointestinal bleeding. It increases the risk of heart failure, kidney failure, and liver failure (Hyllested *et al.,* 2002; Henry *et al.,* 2002). It is used primarily to treat fever, mild to moderate surgery pain, painful menstruation, osteoarthritis, dental pain, headaches, and pain from kidney stones (Davies *et al.,* 1998). Ibuprofen combined with paracetamol is considered generally safe for children for short-term usage (Dahl *et al.,* 2004). The combination of paracetamol and ibuprofen has been found to be efficacious in a variety of acute pain states, including postoperative pain, dysmenorrhoea and musculoskeletal pain (Gazal & Mackie, 2007). The authors concluded that paracetamol and ibuprofen in combination provide better analgesia than the same dose of either drug alone, with fewer patients taking the combination requiring rescue analgesia or experiencing an adverse event (Derry *et al.,* 2013). The aim of this study was to explore the effect of taking paracetamol and ibuprofen in combination for pain relief in children after oral surgery.

Material and methods

This study was conducted at a publicly-funded teaching hospital and a private day-surgical clinic in Zahedan, Iran. It was conducted on children undergoing extraction of at least one lower wisdom tooth with or without one or more upper wisdom teeth by one of three participating surgeons. Patients were excluded from the study if: they were under 10 years old; weighed under 25 kg; had taken any NSAID within 36 h of the operation; had taken medicines containing

acetaminophen or acetaminophen within 12 h of the operation; were taking an angiotensin converting enzyme inhibitor, warfarin, steroid or any immunosuppressive drug; were intolerant of any NSAID or acetaminophen; were suffering from a severe local infection; had a history of peptic ulceration, asthma, or severe haemopoetic, renal or hepatic disease; were participating in the investigation of another experimental agent; or if the clinician believed for any other reason that participation in the study might not be in their best interests. Patients were first approached by the surgeon and then by the study nurse. They were given written and spoken information about the study, and invited to participate. If they consented, patients were then randomized into one of the three study groups in a sequential order to receive one of these formulations, in blinded packs. The randomization sequence was computer generated by the study statistician as a 1:1:1 allocation ratio to the three treatments in a sequence of permuted blocks with stratification for anaesthetic type such as local or general and study centre. Stratification by anaesthetic type ensured a balance between treatments in terms of the number of teeth extracted, as most patients having more than two teeth extracted have a general anaesthetic. Only the statistician had access to the schedule of patient numbers by drug allocation. Participants and investigators were blinded and the randomization code was not broken until the final database had been checked and locked. Children under 8 years old having one or more wisdom teeth removed under general or local anaesthesia were instructed to take two tablets before the operation, then two tablets every 4 h for up to 36 h of a combination of acetaminophen 250 mg and ibuprofen 150 mg per tablet, and acetaminophen 250 mg per tablet alone, and ibuprofen 150 mg per tablet alone. Participants were asked to take two tablets of the study medication before the operation, as close as possible to the start of surgery and then every 4 hours if possible, up to every 6 hours, for up to 48 hours after surgery. All participants were given bupivacaine local anaesthetic blocks by the surgeons. For those participants undergoing general anaesthesia, this was induced with propofol and maintained with isoflurane and nitrous oxide in oxygen. Monitoring was in accordance with the guidelines of the Australian and New Zealand College of Anaesthetists. All extractions were carried out by one of three surgeons, each using his normal technique. If participants required additional postoperative pain relief while in hospital, a rescue dose of fentanyl 10 μg was given as required. After discharge to home, codeine was provided in 30 mg tablets, one to two to be taken as needed up to 4 hourly. Blood samples were obtained from the 38 participants undergoing general anaesthesia in order to have evaluable pharmacokinetic data for at least 30 patients. The first sample was obtained 30 min after the first dose of study medication, the second sample at the end of anaesthesia, and additional one or two samples after the operation in the hospital. The plasma concentration of

acetaminophen and ibuprofen were measured by the sponsor and used to form individual time–concentration profiles. The analytical method used an HPLC Diode Array Detector assay for the simultaneous determination of acetaminophen and ibuprofen in plasma. Precision and accuracy of the acetaminophen and ibuprofen assay were validated over the concentration range 0.5–50 μg ml−1 for both drugs. The intra- and inter-batch precision of the assays at low, medium, and high concentrations of acetaminophen and ibuprofen varied from theoretical values by less than 15%. The lower limit of quantification for each drug was 0.5 μg ml−1. The sponsor monitored all data collected during the study and queries and corrections were made when any inaccuracies or inconsistencies were identified. The primary outcome measure was the area under the curve of the 100 mm visual analogue scale of pain measurement taken for up to 36 h after surgery, divided by time, at rest and in activity. Pharmacokinetic data were collected from a subset of patients. The data obtained were analysed using SAS version 9.1. Efficacy analyses were conducted on an ITT basis with the additional provision that there were at least three VAS measurements over at least 12 h available to calculate the primary endpoint. All participants who were randomized into the study were included in the safety evaluations. As the first dose of study medication was taken before the operation and while under the supervision of the surgeon, all randomized patients took at least a single dose of study medication. A last observation carried forward approach was used for those subjects who left the study prematurely for non-AUC based variables. We compared the primary endpoint between the combination group and each of the acetaminophen and ibuprofen arms, at rest and in activity, using a general linear model (GLM) of SAS software version 9.1 which included terms for treatment, the centre, and anaesthetic stratum. Additionally, to confirm the consistency of treatment effects across strata, the stratum treatment interaction terms were tested and included in the final model. The analysis was also checked with the number of teeth extracted as an additional factor. Continuous secondary efficacy endpoints were tested for significance using the same models as used for the primary endpoint. A one tailed ($P \leq 0.05$) test was pre-specified to indicate statistical significance.

Result and Discussion

The time adjusted AUCs were substantially and significantly lower at rest and in activity in the combination group than in either of the other two treatment groups (Table 1) with all four ($P<0.01$).

Table 1. Mean of time-adjusted AUC of visual analogue pain scores at rest and in activity by treatment groups

------	Paracetamol N=40	Ibuprofen N=40	Combination N=40
Rest	34	35	23
Activities	45	41	29

The differences between combination and each constituent were significant at rest (vs acetaminophen P=0.007 and vs ibuprofen P=0.003) and on activity (vs acetaminophen P=0.006 and vs ibuprofen P=0.007

Although all four secondary endpoints favour the combination treatment (Table 2), only the global pain rating reached statistical significance. More participants experienced 'nil' or 'mild' pain with the combination (68.4%) than with either other group; this difference was significant for acetaminophen (37.5%; P=0.008), but not for ibuprofen (54.3%; P=0.263). The use of any rescue medication also favoured the combination treatment (Table 3), but this did not reach statistical significance.

Table 2. Secondary efficacy endpoints by treatment groups

Global pain rating [n (%)]	Paracetamol	Ibuprofen	Combination
Nil	3(7.5)	4(11.4)	4(10.5)
Mild	22(30.0)	14(42.9)	12(57.9)
Moderate	12(55.0)	15(40.0)	22(31.6)
Severe	3(7.5)	2(5.7)	0(0.0)
Global pain rating [n (%)]			
Nil	26(65.0)	25(71.4)	30(79.0)
Mild	10(25.0)	8(22.9)	7(18.4)
Moderate	3(7.5)	2(5.7)	1(2.6)
Severe	1(2.5)	0(0.0)	0 (0.0)
Vomiting episodes (*n*)	5	0	0

The only significant difference was between the global pain ratings for combination and acetaminophen (P=0.008, Mann–Whitney U-test)

Table 3. Rescue analgesia by groups

Rescue analgesic	Paracetamol	Ibuprofen	Combination
Fentanyl in hospital	5 (11.6%)	9 (23.7%)	6 (15.4%)
Codeine in the first 24 h	21 (47.70%)	16 (43.20%)	13 (32.50%)
Codeine in the second 24 h	22 (53.70%)	14 (42.40%)	16 (42.10%)
Any rescue medication over 48 h	25 (62.5%)	18 (58.10%)	21 (56.8%)

We demonstrated that patients using the combination of acetaminophen and ibuprofen experienced less pain during the first 48 h after oral surgery than those using the same daily dosage of either agent alone and we think the difference was clinically relevant. There was no evidence of any pharmacokinetic interaction between acetaminophen and ibuprofen. Patients receiving ibuprofen alone reported the lowest frequency of adverse events, but the numbers are too small for meaningful comparisons between the groups, and we saw no cause for concern in any group. The current study obtained data that were consistent with previous evidence showing that a combination of ibuprofen and acetaminophen provides better analgesia than acetaminophen alone. However, two of these studies were on children, so data on adults are relatively limited. On the other hand, there are many studies supporting the more general point that the addition of various NSAIDs improves the pain relief obtainable from acetaminophen alone. More importantly, our data add convincingly to the sparse evidence supporting the more controversial proposition that this combination is superior to ibuprofen alone. In a smaller study in an orthopaedic pain model which was positive for the combination in comparison with acetaminophen, Dahl and colleagues (2004) showed that there was no such benefit whereas Viitanen and colleagues (2003) showed an advantage for the combination only in the period after discharge from hospital. The similarity in efficacy between ibuprofen and acetaminophen on their own seen in our study contrasts with the findings of superior pain relief from ibuprofen after dental surgery by Cooper and colleagues (1989) but theirs was a single-dose study.

Conclusion

In conclusion, we could also demonstrate that the doctors treating pain after oral surgery, in hospital and at home, and probably pain in many other situations should consider using acetaminophen and ibuprofen together 6 times a day, provided there are no contraindications to either drug, and taking into account the known risks of NSAIDs. The combination formulation studied here simplifies this regimen. Additionally, more studies in the future are needed for further explanation.

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