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Pre-emptive analgesia reduces postoperative pain experience following oral day case surgery

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Modern concepts of acute pain generation emphasize that surgical trauma may lead to hyperexcitability of dorsal horn sensory neurones, resulting in amplification and prolongation of postoperative pain; these effects may be reduced or eliminated by pre-emptive analgesics. Thirty patients undergoing day case general anaesthetic surgical removal of impacted mandibular third molar teeth were entered into a double-blind, placebo-controlled, randomized study and instructed on the use of the visual analogue scale (VAS) for pain assessment. Patients received one of three test solutions (tramadol 100 mg, ketorolac 30 mg or placebo) intravenously after anaesthetic induction and VAS scores were measured every 30 min for 2.5 h postoperatively. Results confirmed that preoperative administration of tramadol reduced pain experience postoperatively, compared with placebo; comparison with preoperative ketorolac revealed reduced pain scores during the later postoperative period, fewer patients requiring additional analgesics in the initial recovery period and a longer time before first dose 'escape analgesia'.

Key words: Day surgery, pre-emptive analgesia, postoperative pain

Introduction

Recent clinical studies have shown that patients often experience sub-optimal analgesia following surgical procedures[1,2]; effective treatment of postoperative pain is a major priority for clinical research in surgical practice, not only to improve patient comfort but also to ensure satisfactory outcome following the surgical stress response[3]. Recent advances in our understanding of acute pain physiology have introduced the concept of pre-emptive analgesia[4]; analgesia administered prior to painful surgical stimuli is believed to prevent or reduce subsequent pain development[5].

Pathophysiological studies suggest that the nervous system does not modulate all pain in a fixed manner, but rather can respond to some stimuli with a degree of plasticity; once induced such neuroplasticity may sustain and magnify the pain experience[6]. Surgical tissue damage leads to a dual phenomenon of central and peripheral nerve sensitization; central sensitization, mediated via N-methyl-D-aspartic acid (NMDA) receptors in the dorsal horn, prolongs and increases sensitivity to noxious stimuli over an expanded receptive field (hyperalgesia) and results in pain from previously innocuous stimuli (allodynia). Repetition of such stimuli leads to a progressively escalating degree of hyperexcitability termed 'wind up'[4].

Peripheral sensitization, via chemical mediators such as leukotrienes, bradykinin, histamine, arachidonic acid metabolites and sympathetic activity, may occur at the site of injury and surrounding tissue leading to localized hyperalgesia[4].

Pre-emptive analgesia should therefore be possible with agents which interfere with such central and peripheral mechanisms. Indeed, premedication with intravenous opioids has been shown to reduce postoperative pain, presumably by preventing central sensitization, following orthopaedic and abdominal surgery[7,8]. Similarly, non-steroidal anti-inflammatory drugs (NSAIDs) given before surgery have been shown to have postoperative analgesic effects[9,10].

The surgical removal of impacted mandibular third molar teeth can result in intense postoperative pain[11], and indeed, has become an internationally accepted clinical pain model. The aim of this investigation was to assess the extent of pain reduction after third molar surgery when either tramadol (an opioid centrally-acting analgesic) or ketorolac (NSAID) was administered intravenously preoperatively, compared with control groups, and to identify any significant adverse effects.

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Materials and methods

Thirty patients (22 female, 8 male; mean age 23 yr; ASA class I fitness) undergoing day case general anaesthesic surgical removal of impacted mandibular third molar teeth were, following local ethics committee approval, entered into a double-blind, placebo-controlled, randomized study and instructed on the use of the visual analogue scale (VAS) for pain assessment.

Patients were randomly allocated to receive one of three test solutions (tramadol 100 mg, ketorolac 30 mg or placebo) administered as 10 ml over 1 min immediately after anaesthetic induction (5 min before commencement of surgery). A standardized anaesthetic regime (without the use of intraoperative analgesics) was utilized throughout and surgical procedures, which all required the removal of bone prior to tooth disimpaction, were similarly standardized and performed by the same surgeon. VAS pain scores were measured at 30, 60, 90, 120 and 150 min postoperatively; soluble ibuprofen 400 mg was made available as 'escape analgesia'.

Respiratory function was assessed by pulse oximetry measurement of haemoglobin oxygen saturation levels intraoperatively, continuously postoperatively for 10 min and then at 15 and 30 min postoperatively. Similarly, intraoperative recordings were made of pulse and blood pressure and any significant changes in pulse rate or blood pressure noted.

Any other adverse effects were also recorded, such as excessive bleeding intra- or postoperatively and the occurrence of nausea and vomiting during the recovery period.

Results

Figure 1 confirms that VAS pain scores were highest for the placebo group throughout the postoperative period; whilst pain experience for all three groups was similar in the initial postoperative period, tramadol patients demonstrated significantly lower pain scores between 90 and 150 min postoperatively. Statistical comparison at 120 min, for example, revealed a significant reduction in pain scores between tramadol and placebo groups (P = 0.02; Wilcoxon's non-parametric testing).

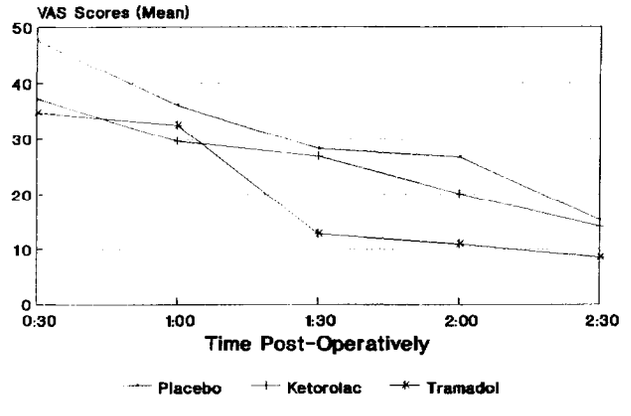

Figure 1. Pain scores.

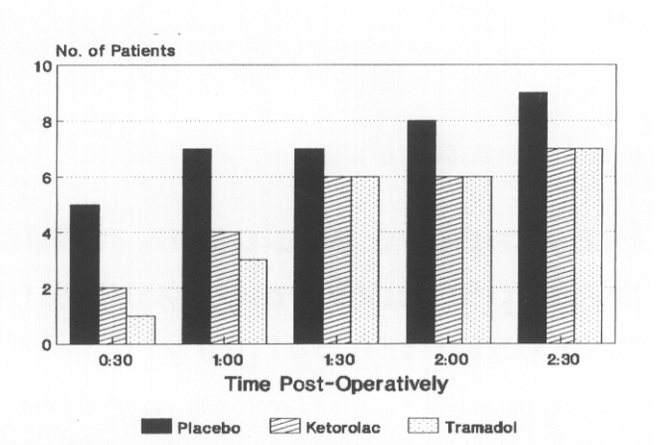

Figure 2. Use of escape analgesia.

Figure 2 illustrates that more placebo patients required 'escape analgesia' throughout the postoperative period than either ketorolac or tramadol patients, whose demands for additional analgesia were very similar, except during the first 60 min postoperatively when slightly more ketorolac patients required 'escape analgesia'.

Table 1 demonstrates that the mean time to receiving 'escape analgesia' was shortest for the placebo group (53 min) and longest for the tramadol group (66 min).

Figure 3 compares haemoglobin oxygen saturation intraoperatively and postoperatively for the three experimental groups. Whilst there were no significant differences in respiratory function between placebo and tramadol patients, statistical analysis confirms that at 15 min post-operation the ketorolac patients exhibited significantly lower oxygen saturations compared with the placebo group (P = 0.03; Wilcoxon's non-parametric testing).

Table 1. Time to first does escape analgesia

	Mean time (min)	Range (min)
Placebo group	53	10–150
Ketorolac group	60	25–140
Tramadol group	66	30–150

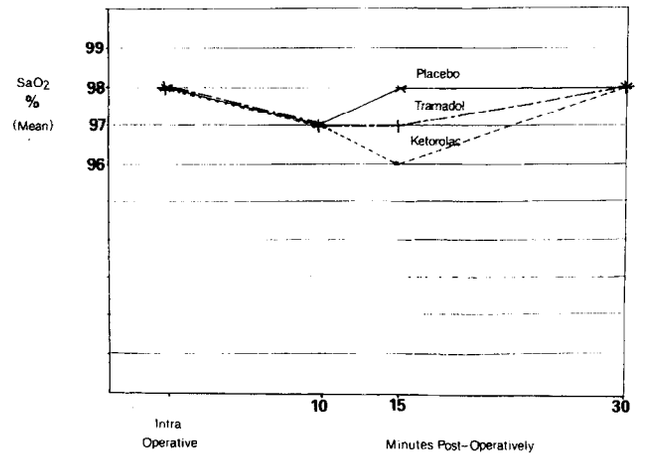

Figure 3. Oxygen saturations.

Adverse effects were recorded in each experimental group: 30% of the placebo patients demonstrated significant increases in heart rate and/or blood pressure during the surgical procedure; significant change was deemed to occur if the heart rate increased by >40 beats per min or the diastolic blood pressure rose to 100 or above. Such changes were presumed to result from inadequate intraoperative analgesia. Thirty per cent of ketorolac patients were noted to bleed excessively intraoperatively, whilst a further 10% bled excessively during the postoperative period. Sixty per cent of tramadol patients reported dizziness between 120 and 150 min postoperatively; this contrasts with 0% for the placebo group and 20% for the ketorolac group (at 30–60 min postoperatively).

Discussion

Tramadol is a centrally acting analgesic of the opioid agonist type that can relieve moderate to severe pain and has been demonstrated to be an effective postoperative analgesic[12,13]. In comparison to other centrally acting agents, negligible respiratory depressant activity has been reported[12]; other side-effects such as constipation, impaired micturition, euphoria and dependency are believed to be rare.

Immediate relief of acute postoperative pain requires parenteral analgesic administration and 100 mg tramadol has been shown to be the optimal dose[14]. In this study tramadol 100 mg was administered intravenously as a centrally acting pre-emptive agent prior to third molar surgery and provided improved pain relief compared with placebo, although this effect appeared most significant between 90 and 150 min post-surgery. Fewer tramadol patients required 'escape analgesics' throughout the postoperative period, compared with the placebo group; such reduction in the consumption of escape medication following tramadol administration has been reported previously[14].

Pulse oximetry assessment of respiratory function revealed no significant depressant effects of tramadol, either intraoperatively or in the immediate postoperative period, compared with placebo patients, which supports previous reports of negligible respiratory depression[15]; this is clearly advantageous for patients undergoing surgery of the upper aerodigestive tract on a day-stay basis.

The main disadvantage of tramadol in this study was the high incidence of reported dizziness, especially common between 120 and 150 min postoperatively. Dizziness, nausea and trembling are amongst the recognized side-effects of tramadol[16]; their occurrence 2 h post-surgery might well limit the usefulness of this agent for day-case patients likely to be discharged 2–3 h postoperatively.

Ketorolac is a non-steroidal anti-inflammatory agent recommended for short-term management of moderate to severe, acute postoperative pain, and which exhibits no opioid related side-effects[17,18]; its peripheral mode of action is to inhibit the cyclo-oxygenase enzyme system and hence prostaglandin synthesis. The analgesic efficacy of ketorolac has been demonstrated to be comparable to morphine and superior to ibuprofen, paracetamol or codeine preparations/combinations in recent clinical trials[19–21]. In this study patients received 30 mg ketorolac intravenously in the immediate preoperative period and exhibited reduced pain scores throughout the observed period and required less 'escape analgesics' compared with control patients, although in the latter postoperative period patients receiving tramadol experienced least pain.

Recent reports, however, have emphasized potentially serious and even fatal adverse reactions associated with the use of ketorolac, including gastrointestinal ulceration and haemorrhage, renal impairment and anaphylaxis[22]. Recommendation has thus been made to reduce the parenteral starting dose to 10 mg, with subsequent doses of 10–30 mg available at 4–6 hourly intervals.

Forty per cent of patients receiving preoperative ketorolac were reported to exhibit excessive bleeding either intraoperatively or immediately postoperatively; ketorolac is known to inhibit platelet aggregation and prolong bleeding time and postoperative wound haemorrhage has been reported following perioperative parenteral use[17]. Strict haemostasis is an important principle in day-case surgery and the potent anti-platelet effects of NSAIDs have previously been cited as possible contraindications in their perioperative use[22,23].

It is interesting that pulse oximetry confirmed a reduction in oxygen saturation in patients receiving ketorolac 15 min postoperatively because it is currently believe that NSAIDs do not cause respiratory depression[23]; despite statistically demonstrated significance, the clinical relevance of a mean oxygen saturation of 96% (range 94–98%) compared with 98% for control patients (range 97–99%) remains questionable.

Recent reports have suggested that NSAIDs may also exhibit, in addition to their peripheral effects, central mechanisms of action on dorsal horn nociceptors[24]; possible synergistic effects comprising inactivation of centrally-acting neuroactive substances together with inhibition of prostaglandin synthesis may help explain the well reported efficacy of NSAIDs in managing acute postoperative pain[25].

It is therefore clear that preoperative administration of either tramadol or ketorolac reduces postoperative pain experience following third molar surgery, although both agents demonstrated side-effects which may limit their usefulness for day-case surgery.

The key question, however, in relation to pre-emptive analgesia is whether analgesic intervention before surgery is more efficient than the same intervention following surgery; further research is required in this particular area, together with additional studies to establish optimal selection and timing of analgesic administration.

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