The efficacy of locally applied morphine in post-operative pain after bilateral third molar surgery

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- 1 Recent evidence has hinted at a peripheral site of action of morphine analgesic efficacy.
- 2 Previous studies by the same authors have developed a model for testing local analgesic efficacy by placing drugs into tooth sockets after third molar surgery.
- 3 The present studies test the hypothesis of local morphine activity at two dosage concentrations, 100 ng ml⁻¹ and 100 µg ml⁻¹ after third molar surgery.
- 4 No significant analgesic efficacy was found at either dose when compared with placebo.

Keywords analgesia morphine peripheral action

Introduction

Morphine is an opioid analgesic used to control severe pain. It is thought to achieve its effect by activating specific opioid receptors in the central nervous system which have been shown to be the site of action of the endogenous opioid pain control mechanism [1].

Previous studies have shown that the efficacy of centrally acting analgesics in the control of post-operative dental pain is poor. Codeine phosphate 30 mg has no significant analgesic advantage over placebo [2], whilst dihydrocodeine 25 mg has been found to induce hyperalgesia after the removal of lower third molars and this effect was increased with the use of dihydrocodeine 50 mg [3]. Pentazocine has been shown to have no advantage over placebo at therapeutic doses up to 100 mg [4, 5].

The efficacy of systemic morphine in post-operative dental pain is uncertain and appears to be route dependent. Intravenous morphine 8 mg gave significant analgesia after the removal of impacted lower third molars [6], whilst oral morphine 20 mg was shown to be ineffective [7].

Opioid receptors have been identified in tissues outside the central nervous system [8] and this gives rise to the possibility that opioid-induced analgesia may be due to some peripheral action. A recent study has developed a method for investigating the site of action of analgesics by placing agents directly into lower third molar sockets. Using this model, local application of both aspirin (100 mg ml⁻¹) and paracetamol (100 mg ml⁻¹) produced significantly more

analgesia than placebo [9]. The present study investigates the efficacy of locally applied morphine in patients with post-operative pain after bilateral lower third molar surgery.

Methods

Two consecutive studies were undertaken for which ethical approval from the local Ethics Committee was obtained. Twenty patients aged 18 to 40 years who required the removal of their bilaterally similar impacted third molars entered the studies, having given written informed consent in accordance with the Declaration of Helsinki, 1971. Patients were excluded from the studies if they had taken any analgesia in the 24 h before surgery, if they had a history of bleeding disorder, renal or hepatic diseases, rheumatic fever or drug hypersensitivity. Pregnant women, or patients who required either steroid or antibiotic cover, were also excluded.

All patients underwent bilateral third molar surgery with an interval of 1 month between each operation. Surgery was carried out by the same operator (U.M.) between 09.000–11.00 h. Local anaesthesia was achieved with 4 ml plain lignocaine [2%]. In all cases 2 ml lignocaine was infiltrated around the inferior dental nerve, and 2 ml around the soft tissues covering the impacted third molar. The tooth was extracted using a standard surgical technique [10], with bone

being removed, where necessary, with burs under saline irrigation. The socket was packed with gauze to achieve haemostasis. Once this had been achieved the gauze was removed. For the first 10 patients, on one occasion the socket was filled with approximately 0.3 ml sterile 10% methyl cellulose gel alone, and on the other occasion with gel containing 100 ng ml⁻¹ morphine sulphate. On the occasion of the placebo treatment, patients were given an oral capsule of 50 ng morphine sulphate at the conclusion of surgery. An oral placebo was given when gel containing morphine was placed in the tooth socket. Treatments were allocated in a blind random fashion.

Due to the cloudy consistency of the morphine gel the operator was aware of the contents of the gel used in this first study, whilst the patient was not. This phase was thus single blind.

The remaining patients completed an identical protocol in which the dosage of morphine was increased 1,000-fold. Thus the concentration of drug in the socket was 100 µg ml⁻¹ and the oral dose of drug was 500 µg. In this study lactose was added to the placebo gel, thus achieving double blind administration.

Post-operatively, all patients were asked to record their pain experience on serial, vertical 10 cm visual analogue scales (VAS) whose boundaries were marked 'no pain' and 'unbearable pain'. Pain recordings were made at 0, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min post-operatively. The recordings obtained from each patient were collated to form a graph of pain against time and the area under the graph was calculated by the trapezoidal method. This measure, expressed in units of mm² h⁻¹ gives an overall recording of each patient's pain experience throughout the 8 h investigation period (AUCs). In the event of poor pain control, patients were permitted to take escape analgesia (ibuprofen 400 mg).

The number of patients requiring escape analgesia per treatment group and the time to dosage was recorded for each treatment regime. If escape analgesia was taken the previous VAS score was extrapolated for all subsequent time points [11]. The patients were reviewed 7 days after surgery when wound healing was assessed.

Student's paired *t*-test was used to assess the differences in pain as expressed by AUCs between local morphine treatment and placebo. Kaplan-Meier estimates of survival distribution function were calculated for the time to first dose of escape analgesia for each treatment group. *P* values of < 0.05 were accepted as statistically significant.

Results

Ten patients received gel containing morphine 100 ng ml⁻¹ and nine completed the study with gel containing morphine 100 µg ml⁻¹. The mean pain scores in each study and their placebo scores are depicted graphically in Figures 1 and 2. Overall pain scores are reported in Tables 1 and 2. There was no significant difference (*P* > 0.05) between both locally

Figure 1 Mean $\pm$ s.e. mean pain scores for patients receiving morphine 100 ng ml⁻¹ (■) or placebo (○) in third molar sockets.

Figure 2 Mean $\pm$ s.e. mean pain scores for patients receiving morphine 100 µg ml⁻¹ (■) or placebo (○) in third molar sockets.

applied morphine treatments and placebo. Most patients took escape analgesia, six out of 10 in the first study and eight out of nine in the second study and again there were no significant differences between placebo and morphine treatments in both studies for either the time to uptake of escape analgesia or the number that required it (Tables 1 and 2). Confidence limits for the mean pain differences are included in Tables 1 and 2.

The local application of morphine at 100 ng ml⁻¹ and 100 µg ml⁻¹ had no adverse effect on haemostasis or healing.

Discussion

The results from our studies show that the local application of morphine, at concentrations of 100 ng ml⁻¹ and 100 µg ml⁻¹ into tooth sockets, in this

Table 1 Pain experience after the local application of morphine (100 ng ml⁻¹) or placebo in third molar sockets

	<i>Placebo</i>	<i>Morphine</i>
Number of patients	10	10
Sex distribution (M:F)	4:6	4:6
Mean pain experience (AUC mm ² h ⁻¹) (s.d.)	262 (82.9)	245 (77.4)
Mean pain difference between treatments (s.e. mean)	17.5 (<i>P</i> = 0.24) (51.9)	
95% confidence limits	-100, 135	
Number of patients requiring escape analgesia	6	6
Median time (min) to uptake of escape analgesia	170	170
range	(620-240)	(45-360)

Table 2 Pain experience after the local application of morphine (100 µg ml⁻¹) or placebo in third molar sockets

	<i>Placebo</i>	<i>Morphine</i>
Number of patients completing study	9	9
Sex distribution (M:F)	3:6	3:6
Mean pain experience (AUC mm ² h ⁻¹) (s.d.)	225 (200)	272 (197)
Mean pain difference between treatments (s.e. mean)	47.7 (<i>P</i> = 0.43) (58.0)	
95% confidence limits	-86.1, 181.4	
Number of patients requiring escape analgesia	8	8
Median time (min) to uptake of escape analgesia	125	105
range	(15-240)	(45-180)

model, shows no clear efficacy in the control of post-operative pain after third molar surgery. Any 'peripheral activity' that morphine may exhibit does not thus appear to result in any antinociceptive effect after this type of surgery. These findings, in part support the evidence that the efficacy of opioids in post-operative dental pain is poor [12].

Other clinical studies, which have evaluated the peripheral antinociceptive actions of morphine and other opioids have produced equivocal findings. This particularly applies to the perineural injection of morphine, with one study reporting positive results [13] whilst others report poor efficacy [14, 15]. By contrast an intra-articular injection of morphine provided significant analgesia after arthroscopic knee surgery [16]. These differences may be related to the functional state of opioid receptors on nerve fibres and on the presence and nature of the localised inflammatory response [17]. The lack of efficacy of morphine when applied to the tooth socket may be related to the nature of the inflammatory response or the impaired functional activity of opioid receptors in the fibres innervating the surgical area. Indeed the presence of opioid receptors in the periodontium and surrounding mucosa is debatable as they have not been identified

in this site, although a preliminary study found that a periodontal ligament injection of 0.5 mg morphine sulphate produced significant analgesia compared with placebo [17]. Even if present it is not certain that all opioid receptors are involved in analgesic responses. Morphine has many pharmacological actions and several receptor sites, for instance in the g.i. tract, where morphine has functional activity divorced from the modulation of pain.

One criticism of the findings from the clinical studies is whether efficacy attributable to locally applied morphine is due to systemic uptake of the drug [19]. To answer such criticism, our study was designed to incorporate a small systemic dose of active drug when the patients had the locally applied placebo. Similarly when active drug was placed in the tooth socket, the patient received a systemic placebo. Both treatment outcomes were practically identical which further substantiates the claim that opioids are of little value in the control of post-operative dental pain.

By contrast to the clinical studies, there is considerable experimental evidence to support the antinociceptive properties of the opioids when applied locally [19]. Local activity of the opioids when

applied locally is reversed by naloxone [6, 17, 20, 21, 22] is dose-dependent and stereospecific. Most studies indicate that mu receptor ligands are the most important agonists, but delta and kappa-ligands are also active, depending upon the nature of the noxious stimuli [23]. Antinociceptive properties of the opioids also appear to be related to the nature and type of experimentally induced inflammatory response, which in turn could influence the activity of the various types of opioid receptors [24, 22].

We can conclude from these studies that local application of morphine has no marked efficacy in the control of post-operative pain after third molar surgery in this model. The lack of efficacy of local morphine in our studies may in part be related to the type of innervation of the surgical area, or impaired expression or lack of activity of opioid receptors. The latter may be influenced by the nature of the inflammatory response which ensues immediately after the surgical procedure.

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