

Pain relief from intra-articular morphine after knee surgery: a qualitative systematic review

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Received 5 September 1996; revised version received 8 January 1997; accepted 15 January 1997

Abstract

Reduction of postoperative pain by injecting opioid into the knee joint is believed to support the hypothesis of peripheral opioid receptor activation in inflammation. The study design consisted of a systematic review of randomised controlled trials (RCTs). Main outcomes were pain intensity and the use of supplementary analgesics. Efficacy of intra-articular bupivacaine against placebo was used as an index of internal sensitivity. Evidence of efficacy was sought in both early (0–6 h after intra-articular injection) and late (6–24 h) periods. Thirty-six RCTs in knee surgery were found. Six had both a local anaesthetic control and placebo; four showed internal sensitivity. All four sensitive studies had at least one outcome showing efficacy of intra-articular morphine against placebo. Six studies compared intra-articular morphine with intravenous or intramuscular morphine or with intra-articular saline without a bupivacaine control. Four of the six studies showed greater efficacy for intra-articular morphine. There was no dose-response evident. No quantitative analysis of pooled data was done. We conclude that intra-articular morphine may have some effect in reducing postoperative pain intensity and consumption of analgesics. These studies had significant problems in design, data collection, statistical analysis and reporting. Trials of better methodological quality are needed for a conclusive answer that intra-articular morphine is analgesic, and that any analgesia produced is clinically useful. © 1997 International Association for the Study of Pain. Published by Elsevier Science B.V.

Keywords: Intra-articular; Opioids; Morphine; Local anaesthetics; Bupivacaine; Knee surgery; Systematic review

1. Introduction

Intra-articular morphine has been used as a clinical test of the hypothesis that peripheral opioid receptors are activated in inflammation (Stein, 1995). The judgement that exogenous opioids can provide effective postoperative analgesia has been taken as confirmation of the hypothesis (Stein, 1995). Even though many studies and reviews have been published on this subject, consensus on whether intra-articular opioids offer clinically relevant pain relief is still lacking.

Particularly important is the issue of the sensitivity of analgesic measurement. Over 40 years ago, Beecher (Beecher, 1955) and Houde (Houde, 1962) described methods for measuring analgesic drugs which were sensitive and reproducible. Sensitive analgesic assays depended upon patients experiencing pain of moderate or severe intensity before test drug administration.

This systematic review, using the evidence from all relevant randomised controlled trials (RCTs), was undertaken to investigate the evidence for an analgesic effect of intra-articular morphine and to examine those features of trial methodology which influence judgement of experimental or clinical effectiveness.

2. Methods

RCTs of intra-articular opioids were sought systematically. A number of different search strategies in both MEDLINE (1966–May 1996), EMBASE and the Oxford Pain Relief Database (1950–1994) were used, without language restriction. Search terms used included ‘intra-articular’, ‘opiates’, ‘opioids’ and ‘morphine’ and ‘random’ (Jadad and McQuay, 1993). Additional reports were identified from the reference lists of retrieved reports and from review articles. Unpublished reports, abstracts and reviews were not considered. Authors were not contacted for original

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data. Reports were considered if they were randomised comparisons of intra-articular morphine with placebo (saline), or different doses of intra-articular morphine, or comparisons of intra-articular morphine with systemic (intravenous or intramuscular) morphine. Reports of direct comparisons of intra-articular morphine and local anaesthetic agents (Khoury et al., 1992; VanNess and Gittins, 1994) were not considered. Reports of pethidine (Ekblom et al., 1993) were not considered because of potential confounding due to its local anaesthetic properties.

Each report which could possibly be described as an RCT was read independently by each of the authors and scored using a 3-item quality scale (Jadad et al., 1996). The scale takes into account proper randomisation, double-blinding and reporting of drop-outs and withdrawals. Consensus was then achieved. Information about the treatments and controls, types of surgery and anaesthesia, number of patients enrolled and analysed, study design, observation periods, outcome measures used for pain intensity and consumption of supplementary analgesics and adverse effects was taken from each report.

Pre-hoc validity criteria were number of patients per treatment group ≥ 10 (L'Abbé et al., 1987), standardised methods of measuring pain intensity, and general anaesthesia. Spinal or epidural anaesthetics were not accepted, nor infiltrations of local anaesthetic into the joints, because we made a post-hoc judgement that low pain scores in the immediate postoperative period could render studies insensitive.

Two periods, early (up to 6 h from the intra-articular injection) and late (from 6 to 24 h) were defined for the evaluation of effectiveness.

Effectiveness was defined as a significant difference (as reported in the original trials) between the active and the control in pain intensity (early and late) or total consumption of rescue analgesics.

There was a pre-hoc agreement that an adequate description of internal sensitivity was a requirement for the demonstration of an analgesic action of intra-articular morphine. Such sensitivity would be derived (not necessarily exclusively) from a statistically significant difference between a known analgesic (intra-articular local anaesthetic) and placebo, from intra-articular morphine being different from placebo, or from a dose-response for intra-articular morphine.

Quantitative analysis of morphine against placebo was planned.

3. Results

Thirty-three RCTs were found in 31 reports, studying nearly 1500 patients (about 900 of whom received morphine). All were in knee surgery. Two reports were in Danish, one in German and the rest in English.

The following papers were excluded: duplicate publica-

tions (Dalsgaard et al., 1993; Lehrberger et al., 1994); the influence of tourniquet time on the efficacy of intra-articular morphine as the only outcome (Klinken, 1995); number of patients per group less than ten (Joshi et al., 1993b; Boden et al., 1994); double-dummy technique not used for intramuscular administration (Björnsson et al., 1994 study 2); control group not blinded (Chan, 1995); controls were intra-articular bupivacaine and unblinded lumbar plexus block only (De Andrés et al., 1993); spinal anaesthesia (Niemi et al., 1994 study 1; Ho et al., 1995); epidural anaesthesia (Raja et al., 1992); operative intra-articular local anaesthetic (Juelsgaard et al., 1993; Dalsgaard et al., 1994; Niemi et al., 1994 study 2; Jaureguito et al., 1995; Reuben and Connelly, 1996); non-standardised anaesthesia (general anaesthesia, spinal or epidural anaesthesia) (Heard et al., 1992); and inadequate standardisation of the timing of pain measurements (Ruwe et al., 1995).

Details of the included studies are shown in Table 1. In all these trials morphine (0.5–5 mg) was used as the intra-articular opioid. Controls used were bupivacaine (0.25–0.5%) as the only intra-articular local anaesthetic, intra-articular saline or intravenous or intramuscular morphine 1–2 mg. No quantitative analysis of pooled data was done because results were presented as means, which are inadequate descriptors of asymmetrically distributed data (McQuay et al., 1996).

3.1. Morphine versus saline in studies where bupivacaine was an index of internal sensitivity (Table 1A)

Six studies compared intra-articular morphine with both bupivacaine and saline (Table 1A). One (Haynes et al., 1994) was only analysed for an early effect (fewer than 10 evaluable patients in the late period).

In two studies (Björnsson et al., 1994; Aasbø et al., 1996), intra-articular bupivacaine could not be differentiated from intra-articular saline and the sensitivity of the analgesic assay was not proven. There was no difference between intra-articular morphine and saline in either.

Four of the trials (Joshi et al., 1993a; McSwiney et al., 1993; Haynes et al., 1994; Karlsson et al., 1995) showed significantly lower visual analogue scale pain intensity (VASPI) scores with intra-articular bupivacaine compared with intra-articular saline during the early period (0–6 h) and so had internal sensitivity.

All four sensitive studies reported early outcomes. Three of the four studies showed significantly lower early pain intensity scores after intra-articular morphine compared with intra-articular saline (Joshi et al., 1993a; McSwiney et al., 1993; Haynes et al., 1994) (Fig. 1A).

In the late period from 6 h onwards intra-articular morphine produced significantly lower pain intensity scores compared with placebo in all three evaluable sensitive studies (Joshi et al., 1993a; McSwiney et al., 1993; Karlsson et al., 1995) (Fig. 1B). Total consumption of supplementary analgesics over 24 h was significantly lower after intra-

Table 1

Studies included

Reference	Comment	Score	Drugs, routes (1–5) and (number of patients)	Results: intra-articular morphine compared with controls				
				VASPI: early bupivacaine	VASPI: late bupivacaine	VASPI: early morphine	VASPI: late morphine	Analgesic consumption: total in 24 h
A. Active control (bupivacaine) and placebo								
Aasbø et al., 1996		3	ia 3 mg M + 20 ml NS (26) ia 0.25% bup 20 ml (27) ia 3 mg M + 0.25% bup 20 ml (27) ia 20 ml NS (27)	No difference between bup and NS at 1, 2, 3 or 4 h	No difference at 8, 24 or 48 h	No difference between M and NS at 1, 2, 3 or 4 h	No difference at 8, 24 or 48 h	No difference
Björnsson et al., 1994a		2	ia 1 mg M + 20 ml NS (21) ia 0.25% bup 20 ml (19) ia 1 mg M + 0.25% bup 20 ml (19) ia 20 ml NS (19)	No difference between bup and NS at 0.5, 1, 1.5 or 2 h	No difference at 8, 24 or 48 h	No difference between M and NS at 0.5, 1, 1.5 or 2 h	No difference at 8, 24 or 48 h	No difference
Haynes et al., 1994	Early included, late excluded (inadequate no. of patients per group)	3	ia 1 mg M + 39 ml NS (10) ia 0.25% bup 40 ml + adr (10) ia 1 mg M + 0.25% bup 39 ml + adr (10) ia 40 ml NS (10)	bup better than NS: at 2 and 4 h $P < 0.05$	$n < 10$	M better than NS: at 2 and 4 h; $P < 0.05$	$n < 10$	$n < 10$
Joshi et al., 1993a		2	ia 5 mg M + 25 ml (10) ia 0.25% bup 25 ml (10) ia 5 mg M + 0.25% bup 25 ml (10) ia 25 ml NS (10)	bup better than NS at 1, 2, 4 h	nsd (8 or 24 h)	M better than NS at 1, 2, 4 h	M better than NS at 8, 24 h	Significance is not mentioned
Karlsson et al., 1995		4	ia 1 mg M + 20 ml (10) ia 0.375% bup 20 ml (10) ia 1 mg M + 0.375% bup 20 ml (10) ia 20 ml NS (10)	bup better than NS at 2, 4, 6 h	nsd (24 or 48 h)	nsd (2, 4, 6 h)	M better than NS at 24, 48 h	M better than NS (0-24 h and 24-48 h)
McSwiney et al., 1993		2	ia 5 mg M + 25 ml NS (10) ia 0.25% bup 25 ml (10) ia 5 mg M + 0.5% bup 12.5 ml + 12.5 ml NS (10) ia 25 ml NS (10)	bup better than NS at: 0.5, 1, 1.5, 2, 4 h	bup better than NS at 8, 12 h	M better than NS at 0.5, 1, 1.5, 2, 4 h	M better than NS at 8, 12, 24 h	M and bup sig ($P < 0.05$) better than NS
B. Placebo but no local anaesthetic as active control								
Joshi et al., 1992		2	ia 5 mg M + 25 ml NS (10) ia 25 ml NS (10)			ia M better than ia NS at 0, 0.5, 1, 1.5, 2 and 4 h; $P < 0.05$	ia M better than ia NS at 8 and 12 h; $P < 0.05$	ia M better than ia NS; $P < 0.05$
Joshi et al., 1993c		2	ia 5 mg M + 25 ml NS (10) ia 25 ml NS (10)			nsd (1, 2 or 4 h)	nsd (8 or 24 h)	ia M better than ia NS, $P < 0.01$
Lyons et al., 1995	Pethidine arm not considered	3	ia 5 mg M + 25 ml NS (20) ia 25 ml NS (20) ia 50 mg pethidine + 25 ml NS (20)			ia M better than ia NS at 0, 0.5, 1, 2 and 4 h; $P < 0.01$	ia M better than ia NS at 8, 12 and 24 h; $P < 0.01$	No difference
C. Cross-route comparisons								
Dierking et al., 1994		4	ia 2 mg M + 40 ml NS + im 1 ml NS (18) im 2 mg M + ia 40 ml NS (15)			nsd (1, 2, 4, 6 h)	Not evaluated	Not evaluated
Hege-Scheuing et al., 1995		3	ia 1 mg M in 10 ml NS + 10 ml NS iv (29) iv 1 mg M in 10 ml NS + 10 ml NS ia (30)			nsd (1, 2, 3, 4, 6 h)	nsd (8 or 24 h)	No difference

Table 1 (continued)

Reference	Comment	Score (1–5)	Drugs, routes and (number of patients)	Results: intra-articular morphine compared with controls				
				VASPI: early bupivacaine	VASPI: late bupivacaine	VASPI: early morphine	VASPI: late morphine	Analgesic consumption: total in 24 h
Stein et al., 1991		2	ia 0.5 mg M in 40 ml NS + iv 1 ml NS (10) ia 1 mg M in 40 ml NS + iv 1 ml NS (18) ia 1 mg M + 0.1 mg naloxone in 40 ml NS + iv 1 ml NS (9) ia 40 ml NS + iv 1 mg M (15)			ia M better than iv M at 3, 4, and 6 h; $P < 0.05$	nsd (24 h)	ia M better than iv M
D. Morphine dose-response (see also Stein et al., 1991 [28])								
Allen et al., 1993		5	ia 1 mg M in 30 ml NS (30) ia 2 mg M in 30 ml NS (30) ia 0.25% bup 30 ml (30) ia 1 mg M in 0.25% bup 30 ml (30)					
Heine et al., 1994		2	ia 1 mg M in 0.5% bup 20 ml (10) ia 3 mg M in 0.5% bup 20 ml (10) ia 20 ml 0.5% bup (11)					
Laurent et al., 1994		4	ia 2 mg M in 0.25% bup 40 ml (20) ia 5 mg M in 0.25% bup 40 ml (20) ia 0.25% bup 40 ml (18)					

ia, intra-articular; no., number; M, morphine; bup, bupivacaine; NS, normal saline; adr, adrenaline; nsd, no significant difference. 'better than' means stated as significant by the authors. P values quoted if given in the paper.

articular morphine compared with saline in the two sensitive studies which analysed it (McSwiney et al., 1993; Karlsson et al., 1995).

3.2. Morphine versus saline, no active (bupivacaine) control (Table 1B)

Three studies compared only intra-articular morphine with intra-articular saline (Joshi et al., 1992; Joshi et al., 1993c; Lyons et al., 1995).

In the early period morphine VASPI scores were significantly lower in two of the three studies which reported early outcomes (Joshi et al., 1992; Lyons et al., 1995) (Fig. 1C).

In the late period, the same two studies (Joshi et al., 1992; Lyons et al., 1995) indicated that intra-articular morphine produced significantly lower pain intensity scores compared with saline. Two of the three studies (Joshi et al., 1992, 1993c) had significantly lower total consumption of analgesics over 24 h after morphine.

3.3. Morphine versus systemic morphine control (Table 1C)

Three studies compared intra-articular with intravenous

or intramuscular morphine (Stein et al., 1991; Dierking et al., 1994; Hege-Scheuing et al., 1995).

In the early period one showed greater efficacy of intra-articular morphine compared with 1 mg intravenous morphine (Stein et al., 1991) (Fig. 1C).

In the late period, no study indicated that intra-articular morphine had statistically lower pain intensity scores, though one had no evaluations beyond 6 h (Dierking et al., 1994) (Fig. 1D). Lower total consumption of analgesics over 24 h was found in only one study (Stein et al., 1991).

3.4. Combination of morphine plus bupivacaine versus saline (Table 1A)

All four sensitive studies which compared intra-articular morphine with both saline and bupivacaine also included a group with a combination of intra-articular morphine plus bupivacaine. All the studies which were sensitive to bupivacaine alone and showed a positive effect for morphine also showed a significant effect for the combination compared with placebo, both early and late (Joshi et al., 1993a; McSwiney et al., 1993; Haynes et al., 1994; Karlsson et al., 1995). The two studies which were insensitive for bupiva-

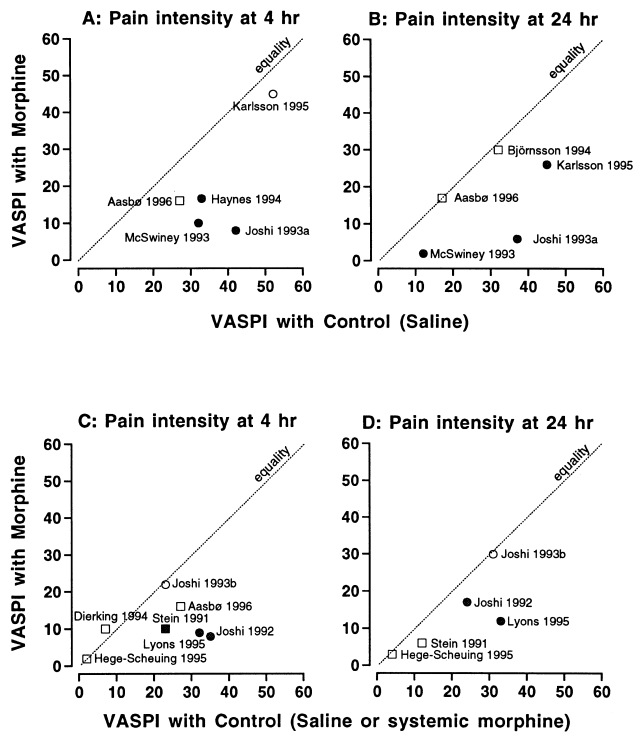


Fig. 1. Mean visual analogue scale pain intensity (VASPI, mm) for intra-articular morphine versus control. Each point represents an individual trial (L'Abbé et al., 1987). Internal sensitivity was assumed when intra-articular bupivacaine was significantly better than saline. A and B: Studies with active (local anaesthetic) control. Circles, sensitive studies; squares, insensitive studies; solid circles, morphine significantly better than saline. C and D: Studies without active (local anaesthetic) control. Circles, placebo control; squares, systemic morphine control; solid symbols, morphine significantly better control.

caine and morphine showed no efficacy for the combination (Björnsson et al., 1994; Aasbø et al., 1996).

3.5. Dose response (Table 1D)

Two studies addressed the question of a dose response with intra-articular morphine alone (Stein et al., 1991; Allen et al., 1993). One study (Stein et al., 1991) could differentiate 1 mg intra-articular morphine, but not 0.5 mg, from control; it could not differentiate 0.5 mg from 1 mg of morphine. The other (Allen et al., 1993) showed a reversed dose response between 1 and 2 mg. Neither had evidence of internal sensitivity.

Two studies compared different doses of morphine in combination with a standard dose of bupivacaine (Heine et al., 1994; Laurent et al., 1994). No dose response was detected between either 1 and 3 mg, or 2 and 5 mg morphine.

3.6. Adverse effects

No adverse effects that could have been attributed to the intra-articular treatment were reported.

4. Discussion

These reports of intra-articular morphine emphasise the importance of considering potential bias and issues of validity in clinical studies before interpreting results.

4.1. Bias

It is now well recognised that studies which are either not randomised or randomised without concealment of treatment allocation, or which are not adequately blinded result in an over-estimation of the effect of treatment (Schulz et al., 1995). Method and concealment of randomisation, double blinding and description of withdrawals and drop-outs were inadequately described in all these studies. The method of randomisation was explicit in three studies (Allen et al., 1993; Laurent et al., 1994; Karlsson et al., 1995). In many it was unclear who was blinded.

4.2. Design and validity

Classic analgesic trial design includes both active and placebo controls. The reason is to ensure that if no difference is found between test analgesic and placebo, the correct interpretation of a negative result can be made if the standard (active control) analgesic gives a significant difference from placebo. This is particularly important when pain is of only mild to moderate intensity. The mean pain intensities after placebo were with one exception less than 50% of the maximum possible (Karlsson et al., 1995), both early and late, and frequently below 25% of maximum (Fig. 1). If there is no pain, reduction in pain intensity cannot be measured. The reduced sensitivity of analgesic studies with low pain intensity has been evaluated (Stubhaug et al., 1995).

Studies which used spinal or epidural anaesthesia were excluded. The reason was that these patients have very low pain intensity scores immediately after operation (Heard et al., 1992) with mean visual analogue scores below 20 mm for 6 h. In their analysis, pain intensity scores after spinal anaesthesia did not approximate those after general anaesthesia until 24 h.

We chose a hierarchy of evidence. The highest rank was when active (bupivacaine) control was used as well as placebo, and analgesic efficacy of intra-articular morphine was interpreted only when intra-articular bupivacaine was better than placebo (i.e., established internal sensitivity). Intra-articular bupivacaine is known to provide reliable analgesia of predictable duration following knee surgery (Chirwa et al., 1989; Kaeding et al., 1990) and it was therefore a valid active control.

4.3. Outcome measures

The special feature of these studies was that necessarily the intervention was made before the patient had pain, analogous to pre-emptive studies (McQuay, 1995). The VASPI

levels were low for several reasons. Diagnostic arthroscopies were included in the primary studies, and opioids and NSAIDs were given both pre- and peroperatively. Diagnostic arthroscopies may not cause enough postoperative pain to be sufficiently sensitive for an analgesic assay. Fig. 1 indicates that studies which were sensitive generally had VASPI levels above 30% of the maximum possible VASPI in the control group in the early period (and most had high VASPI values in the late period also). We excluded studies which used spinal or epidural anaesthesia or infiltration of the knee joint with high doses of local anaesthetic because these measures further reduce postoperative pain and hence sensitivity.

VASPI was usually measured at rest; sensitivity might have been increased by assessing VASPI on movement. Arthroscopic surgery is usually performed as day-case surgery. Sensitivity might have been increased by following the patients in hospital for a longer period. Patients were instructed in the use of VASPI before anaesthesia in only a minority of studies. Most patients were sent home with a questionnaire within 2–6 h from the end of surgery. Few studies mentioned that VASPI assessment was done by a trained, or even the same, observer. All these issues should be addressed in study design. Sensitivity of the analgesic assay is crucial.

Consumption of supplementary analgesics within the first 24 h after surgery was the second commonest outcome measure, but usually not standardised. Other indicators of pain and pain relief, such as time to first analgesic, time to weight bearing, time to discharge, were also used, but only in a minority of studies. VASPI and the total consumption of supplementary analgesics were therefore used as primary outcome measures in the analysis.

4.4. Early and late periods

Analysis by early and late periods was used for several reasons. During the first 2–6 h patients were still in hospital where VASPI measurements were made by researchers or (trained) nurses at predetermined intervals. Secondly, the effect of intra-articular bupivacaine, the index of internal trial sensitivity, should have been most pronounced during this time. Thirdly, any systemic effect of morphine should have been obvious during this period rather than later. The late period was considered to be important as several studies suggested a prolonged effect of intra-articular morphine. Most studies provided information on VASPI values at 24 h and consumption of supplementary analgesics was reported as a total amount taken in 24 h.

No biological reason for suspecting a late rather than an early effect was apparent in the original study on intra-articular morphine (Stein et al., 1991). That indicated that 1 mg of intra-articular morphine provided significantly better analgesia after knee surgery than the same dose given intravenously at 3, 4 or 6 h. No difference was found between the VASPI values at 24 h, although the total con-

sumption of supplementary analgesics during the 24 h period was significantly less after intra-articular morphine.

4.5. Studies with both active and placebo controls

Only six studies included groups receiving saline, bupivacaine and morphine. Four of them were sensitive as defined by significant analgesic effect of bupivacaine compared with saline. All four demonstrated significant analgesic effect of intra-articular morphine compared with placebo at both early and late times (Fig. 1). This provides some evidence for a prolonged biological effect of morphine in the knee joint. The two negative studies (Björnsson et al., 1994; Aasbø et al., 1996) failed the sensitivity test.

4.6. Studies with no active control

Three studies of morphine against saline showed an analgesic effect, two in the early period and all three in the late period. Comparisons of intra-articular with intravenous or intramuscular morphine were less compelling; only one (Stein et al., 1991) of the three showed a significant effect, both early and late. These results again provide some evidence for an analgesic effect of morphine in the knee joint, while raising the issue of whether this is a systemic as opposed to a local effect.

4.7. Dose-response studies

No dose response was detectable in any study, over a dose range of 0.5–5 mg. The minimum dose tested (0.5 mg) did not show analgesic efficacy (Stein et al., 1991). A dose of 1 mg did (Stein et al., 1991; Haynes et al., 1994; Karlsson et al., 1995). No greater effect was found using morphine doses of 2 compared with 1 mg (Allen et al., 1993). In combination with local anaesthetic, morphine doses of 3 compared with 1 mg (Heine et al., 1994) and 5 compared with 2 mg (Laurent et al., 1994) showed no increased efficacy. None of these studies had proven internal sensitivity. Failure to demonstrate dose response may therefore have been due to lack of sensitivity in the methods.

However, the lowest effective dose used, of 1 mg morphine, would, in a 20-ml injection, be equivalent to a concentration of about 200 $\mu\text{mol/l}$ (50 $\mu\text{g/ml}$). Typical blood or tissue levels after systemic injections of analgesic doses of morphine are found at concentrations of nmol/l, at least 1000 times lower (Moore et al., 1987). The very high concentrations of morphine in the knee joint would be expected to saturate any opioid receptors present. If morphine is acting on local opioid receptors, then the minimal effective dose may well be much less than 1 mg. Failure to demonstrate a dose response might then be because the doses tested were at the top end of the dose-response curve. Late efficacy might be a consequence of residual high morphine concentrations.

4.8. Is intra-articular morphine effective?

Taken together, these results render some support for the hypothesis that intra-articular morphine provides pain relief after knee surgery (Stein, 1995). Using a simple 'vote-counting' approach on Fig. 1, the points from the majority of the trials fall in the lower right quadrant, indicating greater efficacy with morphine than control. Convincing evidence for an early effect is lacking. There was more consistent evidence for a prolonged analgesic effect, mostly a single estimate of pain intensity at 24 h or consumption of analgesic. These are weak measures.

The problem is that this evidence rests on four trials which fulfilled the sensitivity requirements but which had only ten patients per treatment group, and two others which were methodologically weak but did distinguish morphine from saline. Against these studies stands the failure to demonstrate a dose-response for intra-articular morphine.

Overall, the evidence is not compelling. The lessons for future studies are obvious, but the current agenda is one of research rather than clinical utility.

Acknowledgements

This research was supported by European Union Biomed 2 contract BMH4 CT95 0172, NHS Research and Development Health Technology Assessment Programme 94/11/4 and 93/31/4, and NHS National Cancer Research and Development Programme NCP/ICV/I03.

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