Intraarticular fentanyl compared with morphine for pain relief following arthroscopic knee surgery

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Purpose: To compare the analgesia produced by comparable doses of intra-articular (IA) morphine and fentanyl.

Methods: Sixty-nine healthy patients undergoing arthroscopic surgery received a standardized general anesthetic of 4 $mg \cdot kg^{-1}$ thiopental and 2 $\mu g \cdot kg^{-1}$ fentanyl followed by 2 $mg \cdot kg^{-1}$ succinylcholine prior to tracheal intubation and controlled ventilation. Maintenance of anesthesia was achieved with N_2O/O_2 and isoflurane.. At the conclusion of surgery intra-articular injection was: Group I (n=23) 50 μg fentanyl in 20 ml saline; Group II (n=24) 3 mg morphine in 20 ml saline; Group III (n=22) 20 ml saline. Pain scores at rest using a visual analogue scale were recorded by a separate blinded observer at one, two, four, and eight hours postoperatively.

Results: Pain scores at one, two, four, and eight hours were 36, 26.3, 20.9, and 12.8 *vs* 35.8, 33.8, 28.8, and 21.9 *vs* 70.5, 57.7, 58.4, and 53.6 for the IA-fentanyl, IA-morphine, and control groups respectively. Pain scores were greater at all times for Group III. Pain scores for Groups I and II were similar at one hour, but thereafter were less ($P < 0.001$) for the IA-fentanyl group.

Conclusion: Better postoperative analgesia was achieved with 50 μg intraarticular fentanyl than with 3 mg intraarticular morphine.

Objectif : Comparer l'analgésie produite par des doses comparables de morphine et de fentanyl intra-articulaires (IA).

Méthode : Soixante-neuf patients en santé devant subir une intervention arthroscopique ont reçu une anesthésie générale standard avec 4 $mg \cdot kg^{-1}$ de thiopental et 2 $\mu g \cdot kg^{-1}$ de fentanyl suivis de 2 $mg \cdot kg^{-1}$ de succinylcholine avant l'intubation endotrachéale et la ventilation contrôlée. On a maintenu l'anesthésie avec N_2O/O_2 et de l'isoflurane. À la fin de l'opération, l'injection intra-articulaire comprenait : Groupe I (n=23), 50 μg de fentanyl dans 20 ml de solution salée; Groupe II (n=24) 3 mg de morphine dans 20 ml de solution salée; Groupe III (n=22) 20 ml de solution salée. Les scores de douleur ont été notés au repos au moyen d'une échelle visuelle analogue par un observateur impartial distinct à une, deux, quatre et huit heures après l'opération.

Résultats : Les scores ont été à une, deux, quatre et huit heures de 36 - 26,3 - 20,9 - 12,8 *vs* 35,8 - 33,8 - 28,8 - 21,9 *vs* 70,5 - 57,7 - 58,4 - 53,6 pour les patients qui ont reçu du fentanyl IA, de la morphine IA et la solution salée, respectivement. Les scores de douleur ont été plus grands, en tout temps, chez les patients du Groupe III. Les scores de douleur ont été similaires chez les patients des Groupes I et II à une heure, mais moindres par la suite ($P < 0,001$) pour les patients qui ont reçu du fentanyl IA.

Conclusion : Une analgésie plus efficace a été obtenue avec l'injection intra-articulaire de 50 μg de fentanyl plutôt que 3 mg de morphine.

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THE existence of agonist-specific peripheral opioid receptors has been well documented in recent years. The paradigm most commonly used in the clinical study of peripheral opioid action has been surgical arthroscopy. A number of such studies have demonstrated effective and prolonged analgesia from small intraarticular (IA) doses of morphine.[1-8] In contrast, other investigators have failed to demonstrate an analgesic effect of IA morphine.[9-15] There is no explanation for these contradictory findings. One potential confounding variable which may explain the conflicting results is the influence of the degree of inflammation existing preoperatively. Peripheral opioid antinociception has been shown to be most clearly manifested in the presence of local inflammation.[16] The timing of IA morphine instillation may also be a confounding factor. Whitford *et al.* found that maintaining tourniquet inflation for ten minutes following IA morphine injection improved IA morphine postoperative analgesia,[17] presumably by allowing tissue binding prior to tourniquet release and the subsequent post-tourniquet hyperemia and tissue washout.

While morphine is the classic mu-receptor agonist it may be an unfortunate choice for study of the clinical application of peripheral opioid analgesia. Morphine is well known to cause histamine release.[18] Histamine is a powerful activator of nociceptors in the local tissues and induces substance-P release.[19] Histamine and substance P produce vasodilatation and increased vascular permeability, which lead to the release of bradykinin.[19] Substance P promotes additional release of histamine from mast cells and serotonin from platelets.[19] Therefore, a high local concentration of morphine might produce a high local concentration of histamine, in turn setting off a cascade of chemical and physiological changes that create local hyperalgesia. Morphine combined with local anesthetic in both rhinoplasty[20] and carpal tunnel surgery[21] proved antianalgesic. Atanassoff and colleagues found that morphine added to intradermal lidocaine reduced tolerance to thermal stimuli.[22] All of these authors attributed the antianalgesic effect of local morphine to its release of histamine. In contrast, Tverskoy *et al.* found that fentanyl added to lidocaine 0.5% enhanced analgesia by wound infiltraton.[23]

It is possible that the choice of morphine may be responsible for the variable results of clinical trials of peripheral opioid analgesia. We hypothesized that the use of the non-histamine releasing opioid, fentanyl, would provide better peripheral analgesia than would morphine. The purpose of this study was to compare the analgesic effect of IA morphine with that of IA fentanyl, a lipid soluble and non-histamine releasing opioid.

Materials and Methods

The study protocol was approved by the hospital Helsinki Committee of Clinical Investigation and written informed consent was obtained from all patients. Sixty-nine patients between the ages of 18 and 35 yr undergoing arthroscopic knee surgery were included in the study. All patients were ASA physical classification I and all were free of chronic medications.

All patients received 10 mg diazepam *po* at least one hour prior to surgery. General anesthesia was conducted for all patients using an induction regimen of 4 $mg \cdot kg^{-1}$ thiopental and 2 $\mu g \cdot kg^{-1}$ fentanyl followed by 2 $mg \cdot kg^{-1}$ succinylcholine to facilitate tracheal intubation and controlled ventilation. Maintenance of anesthesia was achieved with N_2O/O_2 and isoflurane. No further analgesic or sedative medications were given for the duration of the procedure.

Surgical procedures consisted of arthroscopic removal of torn meniscus, arthroscpic removal of foreign body, debridement of chondromalacia, and diagnostic arthroscopy (Table I). At the conclusion of surgery and after removal of the arthroscope, one of the following solutions was injected intra-articularly in a double-blind manner: Group I (n=23) received 50 μg fentanyl in 20 ml saline; Group II (n=24) received 3 mg morphine in 20 ml saline; Group III (n=22) received 20 ml saline only and served as the control group. The solutions did not contain adrenaline. Group assignments were randomized using a sealed envelope technique. Tourniquet release followed ten minutes after the intraarticular injection, during which time the dressing was applied to the knee.

Postoperatively a 100 mm linear visual analogue scale (VAS) was used to assess the degree of pain at rest. The range of the scale was "0" (no pain) to "100" (unbearable pain). Scores were recorded for each patient at one, two, four, and eight hours after the conclusion of the surgery. Scoring was conducted by an observer blinded to patient group assignment. Postoperative analgesic was available to the patients as 75 mg meperidine *im* every four hours on demand. Patient use of postoperative analgesics was recorded and summarized as total analgesic consumption for the first eight hours postoperatively.

TABLE I Operative arthroscopic procedures

Procedure	*Total*	*IA-Fentanyl*	*IA-Morphine*	*Control*
Menisectomy	34	11	12	11
Debridement	16	6	5	5
Diagnostic arthroscopy	13	4	5	4
Removal of foreign body	6	2	2	2
No. of patients	69	23	24	22

TABLE II Postoperative Pain Scores

	IA-Fentanyl		*IA-Morphine*		*Control*
One hour	36 ± 3.6	*NS*	35.8 ± 4.0	*P < 0.001*	70.5 ± 5.2
Two hours	26.3 ± 3.7	*P < 0.001*	33.8 ± 4.2	*P < 0.001*	57.7 ± 4.5
Four hours	20.9 ± 3.8	*P < 0.001*	28.8 ± 3.40	*P < 0.001*	58.4 ± 5.1
Eight hours	12.8 ± 3.6	*P < 0.001*	21.9 ± 3.8	*P < 0.001*	53.6 ± 5.3

Pain scores represent visual analog scale scores using 100 mm scale; 0="No Pain", 100="Unbearable Pain".
All figures represent Mean ± SD
P values represent significance levels between adjacent columns

Statistical analysis was conducted using GB-Stat (Dynamic Microsystems, Silver Spring , MD). Patient ages for the three groups were compared using one way analysis of variance (ANOVA). Categorical data (gender, type of surgery) were analyzed using contingency table analysis. Pain scores were analyzed both by one way ANOVA and Kruskal-Wallis test.

Results

There were no differences among the groups in terms of age, sex, or arthroscopic procedure. Analgesic consumption was equivalent for the IA-fentanyl and IA-morphine groups as four patients in each group received one dose each of meperidine (mean consumption of 13.0 and 12.5 mg respectively). Analgesic consumption was greater in the saline group where mean meperidine consumption during the study period was 47.8 mg. The saline group had more pain at all times after surgery than either the IA-fentanyl or the IA-morphine group ($P < 0.001$ by both ANOVA and Kruskal –Wallis, Table II). There was no difference between the IA-fentanyl and the IA-morphine group at one hour postoperatively. Thereafter, however, the IA-morphine group reported more pain ($P < 0.001$ by both ANOVA and Kruskal –Wallis) . Pain scores diminished gradually over the testing period for both the IA-fentanyl and IA-morphine groups but did not decrease between two and eight hours postoperatively for the control group.

Discussion

The principal finding of this study was that intraarticular fentanyl provided postoperative analgesia that was superior to that provided by a relatively equipotent dose of intraarticular morphine. Both groups of patients receiving intraarticular opioid had less postoperative pain than the control group who received only intraarticular saline. These findings are in agreement with a growing body of literature regarding the analgesic efficacy of peripheral opioids.

While the results of this study are suggestive, there is no basis to conclude anything more than that 50 μg intraarticular fentanyl is more effective than 3 mg intraarticular morphine. Explanation of these results remains speculative. Our hypothesis suggests that morphine is a less effective peripheral analgesic because of the conflicting influence of local histamine release induced by morphine although we are unaware of data on IA histamine levels following IA morphine. The results of this study, while supporting the hypothesis, must be considered as preliminary. They do not address mechanisms and suggest the need for further study.

Several studies have demonstrated an antianalgesic action of locally instilled morphine.[20–22] Allen *et al.*[6] found that patients who had received 1 mg morphine IA had lower post-arthroscopy pain scores than did patients who had received 2 mg morphine IA. A very low dose of morphine may be sufficient to saturate local opioid receptors, any dose in excess of this having minimal analgesic benefit while causing greater local histamine release. A biphasic response for IA morphine analgesic efficacy would explain the "paradoxical response" noted by these authors. We are not aware of any dose-response studies for intraarticular morphine where this possibilty was explored. Where different doses of intraarticular morphine have been used , for example 1 mg and 5 mg , the results are of doubtful validity because of the failure to give the patients equal systemic doses of morphine (as with a supplemental intramuscular injection).[24] Our choice of 3 mg morphine was based on the range of 1 mg to 5 mg typically reported for IA use although this may not be the optimum IA dose. The use of a smaller dose of morphine may have proved more effective.

It is necessary to consider alternative explanations for our results. Our assumption of analgesic equivalency of 50 μg fentanyl and 3 mg morphine (potency ratio of 60) may have underestimated the relative potency of fentanyl. This ratio may be as high as 100 in which case the fentanyl dose was relatively greater

than the morphine dose and could have accounted for the differences between groups. It is doubtful that a systemic effect of the additional 20 μg of fentanyl accounted for the results, but it is possible that the intraarticular effect of 50 μg as opposed to 30 μg fentanyl did. This question remains unanswered as the dose-response characteristics of IA fentanyl are unknown. One study, whose results directly contradict ours, compared intraarticular morphine with intraarticular fentanyl and found that 20 ml bupivacaine 0.25% with 1 mg morphine provided analgesia superior to that of 20 ml bupivacaine 0.25% with 100 μg fentanyl.[25] We question the results of that study since even at one hour postoperatively, when one would expect comparable analgesia from the IA bupivacaine, there were substantial differences between the two groups. The lack of established dose-response curves for both IA fentanyl and IA morphine makes correlation with our results impossible.

In an attempt to control confounding variables our patient groups were matched not only for patient demographics but also for the type of arthroscopic surgery. Tourniquet times after injection were standardized. Epinephrine was not used in the solution which was given in a standardized volume and all patients had a standardized general anesthetic. All of the patients in this study were hospitalized for 24 hr after surgery thereby eliminating any influence of postoperative activity. All patients received 2 $\mu g \cdot kg^{-1}$ fentanyl *iv* at induction and that may have had an effect to blunt otherwise greater differences between groups through a preemptive analgesia effect.[26] However, differences among groups were highly statistically significant. Postoperative supplemental analgesic use was not likely to have confounded our results as the use of meperidine was comparable in the IA-fentanyl and the IA-morphine groups and was greater in the saline group which, nevertheless, had higher pain scores.

One of the methodological problems that has plagued some studies is that control groups did not receive systemic opioids while the study group did. That is, one cannot assume that the intraarticular opioid does not "wash out" into the systemic circulation and thus exert a systemic effect. In this study we used relatively equipotent doses of fentanyl and morphine to control for this confounding effect. The similar pain scores at one hour may reflect more of a systemic than a peripheral effect for the study drugs. A number of studies of this phenomenon have noted a delayed onset of peripherally mediated analgesia. Thus, only at two hours and beyond did the local action of the opioids predominate.

In summary, this study demonstrated that from two hours postoperatively and beyond, 50 μg fentanyl IA provided postoperative analgesia superior to that of 3 mg morphine IA.

References

1 *Stein C, Comisel K, Haimerl E, et al.* Analgesic effect of intraarticular morphine after arthroscopic knee surgery. N Engl J Med 1991; 325: 1123–6.

2 *Likar R, Schäfer M, Paulak F, et al.* Intraarticular morphine analgesia in chronic pain patients with osteoarthritis. Anesth Analg 1997; 84: 1313–7.

3 *Joshi GP, McCarroll SM, Cooney CM, Blunnie WP, O'Brien TM, Lawrence AJ.* Intra-articular morphine for pain relief after knee arthroscopy. J Bone Joint Surg (Br) 1992; 74: 749-51.

4 *Joshi GP, McCarroll SM, O'Brien TM, Lenane P.* Intraarticular analgesia following knee arthroscopy. Anesth Analg 1993; 76: 333–6.

5 *Dalsgaard J, Felsby S, Juelsgaard P, Froekjaer J.* Low-dose intra-articular morphine analgesia in day case knee arthroscopy: a randomized double-blinded prospective study. Pain 1994; 56: 151–4.

6 *Allen GC, St. Amand MA, Lui ACP, Johnson DH, Lindsey MP.* Postarthroscopy analgesia with intraarticular bupivacaine/morphine. Anesthesiology 1993; 79: 475–80.

7 *Heine MF, Tillet ED, Tsueda K, et al.* Intra-articular morphine after arthroscopic knee operation. Br J Anaesth 1994; 73: 413–5.

8 *McSwiney MM, Joshi GP, Kenny P, McCarroll SM.* Analgesia following arthroscopic knee surgery. A controlled study of intra-articular morphine, bupivacaine or both combined. Anaesth Intensive Care 1993; 21: 201–3.

9 *Laurent SC, Nolan JP, Pozo JL, Jones CJ.* Addition of morphine to intra-articular bupivacaine does not improve analgesia after day-case arthroscopy. Br J Anaesth 1994; 72: 170–3.

10 *Khoury GF, Chen ACN, Garland DE, Stein C.* Intraarticular morphine, bupivacaine, and morphine/bupivacaine for pain control after knee videoarthroscopy. Anesthesiology 1992; 77: 263–6.

11 *Raja SN, Dickstein RE, Johnson CA.* Comparison of postoperative analgesic effects of intraarticular bupivacaine and morphine following arthroscopic knee surgery. Anesthesiology 1992; 77: 1143–7.

12 *Heard SO, Edwards WT, Ferrari D, et al.* Analgesic effect of intraarticular bupivacaine or morphine after arthroscopic knee surgery: a randomized, prospective, double-blind study. Anesth Analg 1992; 74: 822–6.

13 *Badner NH, Bourne RB, Rorabeck CH, Doyle JA.* Addition of morphine to intra-articular bupivacaine

does not imporve analgesia following knee joint replacement. Reg Anesth 1997; 22: 347–50.

14 *Kalso E, Tramer MR, Carroll D, McQuay HJ, Moore RA.* Pain relief from intra-articular morphine after knee surgery: a qualitative systematic review. Pain 1997; 71: 127–34.

15 *Dierking GW, Östergaard HT, Dissing CK, Kristensen JE, Dahl JB.* Analgesic effect of intra-articular morphine after arthroscopic meniscectomy. Anaesthesia 1994; 49: 627–9.

16 *Stein C.* Peripheral mechanisms of opioid analgesia. Anesth Analg 1993; 76: 182–91.

17 *Whitford A, Healy M, Joshi GP, McCarroll SM, O'Brien TM.* The effect of tourniquet release time on the analgesic efficacy of intraarticular morphine after arthroscopic knee surgery. Anesth Analg 1997; 84: 791–3.

18 *Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ.* Histamine release by four narcotics: a double blind study in humans. Anesth Analg 1987; 66: 723–30.

19 *Cousins MJ.* Acute pain and the injury response: immediate and prolonged effects. Reg Anesth 1989; 14: 162–79.

20 *Ben-David B, Moscona RA, Stahl S.* The combination of morphine with local anaesthetic in rhinoplasty – no evidence of a peripheral morphine effect. Acta Anesthesiol Scand 1996; 40: 892–7.

21 *Stahl S, Ben-David B, Moscona RA.* The effect of local infiltration with morphine before carpal tunnel release. J Bone Joint Surg (Am) 1997; 79: 551–4.

22 *Atanassoff PG, Brull SJ, Printsev Y, Silverman DG.* The effect of intradermal administration of lidocaine and morphine on the response to thermal stimulation. Anesth Analg 1997; 84: 1340–3.

23 *Tverskoy M, Braslavsky A, Mazor A, Ferman R, Kissin I.* The peripheral effect of fentanyl on postoperative pain. Anesth Analg 1998; 87: 1121–4.

24 *Kanbak M, Akpolat N, Öcal T, Doral MN, Ercan M, Erdem K.* Intraarticular morphine administration provides pain relief after knee arthroscopy. Eur J Anaesthesiol 1997; 14: 153–6.

25 *Uysalel A, Keçik Y, Kirdemir P, Sayin M, Binnet M.* Comparison of intraaarticular bupivacaine with the addition of morphine or fentanyl for analgesia after arthroscopic surgery. Arthroscopy 1995; 11: 660–3.

26 *Katz J, Kavanagh BP, Sandler AN, et al.* Preemptive analgesia. Clinical evidence of neuroplasticity contributing to postoperative pain. Anesthesiology 1992; 77: 439–46.