Femoral nerve sheath infusion with fentanyl induces analgesia

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Background

- There is a growing body of evidence that supports the concept of peripheral opioid receptors and their contribution to analgesia following opioid administration [1,2].

- We address the theory of peripheral opioid receptors by investigating whether plasma fentanyl levels contribute significantly to analgesia provided by femoral nerve sheath infusions compared to intravenous administration of equal doses.

1. Stein C: Peripheral mechanisms of opioid analgesia. Anesth Analg 1993; 76: 182-91
2. Janson W, Stein C: Peripheral opioid analgesia. Curr Pharm Biotechnol 2003; 4: 270-4

Study Design

- IRB Approved, prospective, double-blinded, randomized study
- 40 patients enrolled

Inclusion Criteria
• Patients undergoing unilateral, primary total knee replacement
• ASA class I-III
• 18 years and older
Exclusion criteria
• Patient refusal
• Pregnancy
• Coagulopathy
• Adverse/allergic reaction to any opioids or local anesthetics
• History of long-term opioid use (greater than 60 days)
• Infection
• Traumatic lower extremity injury
• Body Mass Index (BMI) greater than 35
• No weight-bearing per physician's orders

Study Design: Anesthetic Technique

- In the preoperative area, each patient underwent femoral nerve sheath catheter (StimuCath™, Arrow, Reading, PA) placement.
- All patients received 10ml of 0.1% ropivacaine administered via a single injection sciatic block preoperatively.
- The intraoperative anesthetic regimen was standardized:
  - 1-2mg preoperative midazolam sedation
  - 2 mg/kg of intravenous propofol and 100 µg fentanyl for induction
  - Succinylcholine and or rocuronium neuromuscular blockade was used to facilitate tracheal intubation
  - Sevoflurane and oxygen/air mixture (1:1) for maintenance of anesthesia.
- Intraoperative opioids were limited to the use of morphine sulfate (MSO_4) at a total dosage not to exceed 0.3mg/kg for intraoperative management of pain associated tachycardia and hypertension.
- Upon the patient's arrival to the post-anesthesia care unit (PACU), a PCA pump (Hospira LifeCare PCA III, Lake Forest, IL) was attached to the femoral nerve sheath catheter and a Baxter I PCA pump (Deerfield, IL) was attached to the IV catheter

Study Design: Treatment Arms

- 2 Treatment Arms (20 patients each):
  - A blinded infusion of either fentanyl (3 µg/ml @ 10ml/hr) or normal saline (NS) through the femoral nerve sheath (FNS) catheter.
  - Patients who received fentanyl through their FNS catheter received basal NS as an IV PCA.
  - The patients who received saline through their FNS catheter received basal fentanyl (50 µg/ml @ 0.6ml/hr) through an IV PCA.
- All study drugs were continuously infused for a 24 hour period at a basal rate starting from the time the patient entered the post anesthesia care unit (PACU)

Methods: Post-Operative Pain Assessments

- Postoperative pain levels were assessed using a 0-10cm scale (Visual Analog Scale).
- A series of assessments took place while the patient was resting in bed at the following time points:
  - Upon PACU arrival, followed by every 2hrs for the first 12hrs, then at 16hrs, 20hrs and 24hrs
- One additional pain assessment was recorded on POD1 during the first session of physical therapy while the patient was ambulating.

Methods: Rescue Pain Medication

- During the 24 hour study, patients whom complained of breakthrough pain were given morphine 4 – 8 mg IV every 2 hours as needed until a VAS score of <5 was attained. Total supplemental morphine was calculated for each treatment arm.

- The incidence of opiate induced side effects were documented: nausea, vomiting, constipation, respiratory depression, pruritus and sedation.

Methods: Serum Fentanyl Levels

- At the conclusion of the 24 hour blinded study infusion, all patients had venous blood drawn for measurement of serum fentanyl levels.
- The serum was transported to an outside laboratory for evaluation of the fentanyl level.

Results: Patient Demographics

	FNS Catheter Fentanyl (n = 20)	IV Fentanyl (n = 20)	p-value
Male/ Female	9/11	6/14	0.605
Age (years)	71 (53-85)	65.5 (53-83)	0.618
BMI (m/kg^2)	30.4 (21.6-37.6)	31.2 (18.9-37.1)	0.865
Length of Hospital Stay	4 (2-7)	4 (3-7)	0.257

The values are expressed as median (range). FNS=Femoral Nerve Sheath

- All femoral nerve blocks were successfully placed
- All 40 patients completed the study
- There were no statistically significant differences between the groups with regard to age, weight, or height

Pain During Ambulation was Significantly Reduced with a FNS Fentanyl Infusion Compared to an IV Fentanyl Infusion at same dose and rate

- Pain scores while ambulating were significantly lower in the group that received fentanyl through the FNS catheter compared to patients that received fentanyl through their IV (3.5 vs. 6, respectively; p=0.044).

- No significant differences in resting pain scores

		FNS Catheter Fentanyl	IV Fentanyl	p-value
Pre-Op		3.9 (0-10)	4.0 (0-10)	0.922
Upon PACU Arrival		2 (0-9)	4 (0-9)	0.643
Number of hours post-operation	2	2 (0-8)	2 (0-8)	0.914
	4	0.5 (0-7)	0 (0-5.5)	0.347
	6	1.5 (0-6)	0 (0-5.5)	0.335
	8	2 (0-7)	1 (0-8)	0.519
	10	2 (0-9)	2 (0-7)	0.450
	12	3.5 (0-8)	2 (0-9)	0.979
	16	4 (0-9)	2.5 (0-10)	0.525
	20	3.5 (0-10)	4 (0-10)	0.997
	24	4 (0-8)	3 (0-9)	0.776
Ambulation during first physical therapy assessment		3.5 (0-9)	6 (1-9)	0.044*

VAS Scores are represented as median (range).
*P-values ≤ 0.05 are considered statistically significant.

No Significant Differences in Postoperative Supplemental Morphine Requirements or Opioid Induced Side Effects were found between the groups

Rescue Morphine Requirements in milligrams

	FNS Catheter Fentanyl	IV Fentanyl	p-value
PACU	3 (0-12)	2 (0-14)	0.871
Nursing Floor	12 (0-72)	14 (0-64)	0.413

Data are presented as Median (range).

Number of Patients that experienced nausea and/or vomiting

	FNS Catheter Fentanyl	IV Fentanyl	p-value
Number of Patients (percentage)	9 (45%)	10 (50%)	0.233

Serum fentanyl levels were significantly lower when infused via the FNS catheter compared to the IV catheter group

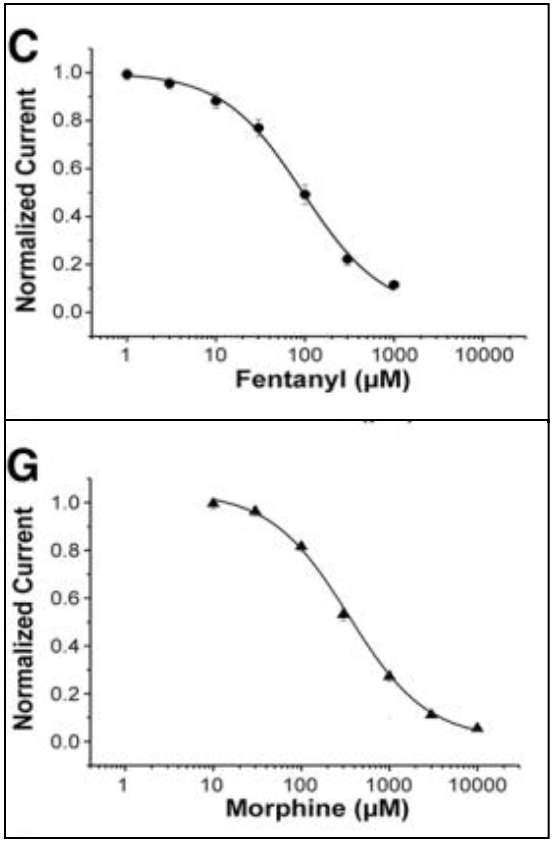
	FNS Catheter	IV	p-value
Fentanyl Level (ng/ml)	0.3 (0-0.8)	0.6 (0-11.2)	p=0.011

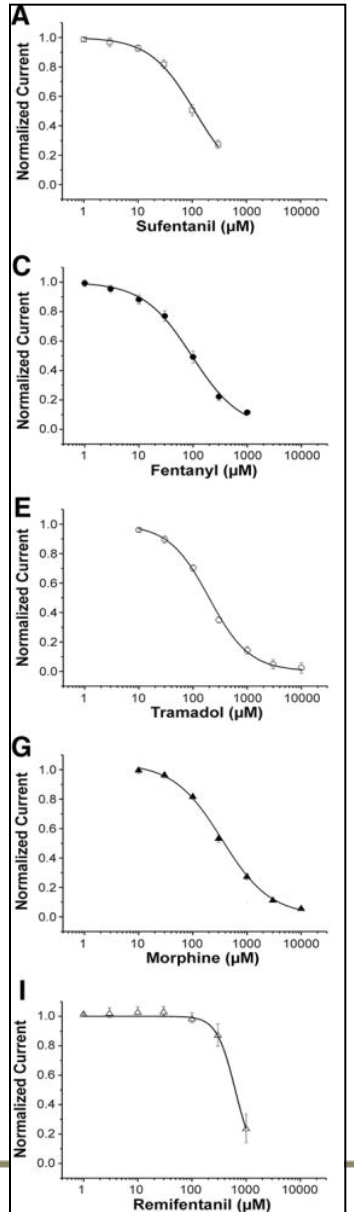
Data are represented as median (range). *P-values $\leq$ 0.05 are considered statistically significant.

The mean minimum effective analgesia concentration for fentanyl is 0.63 ng/ml[4]

Gourlay GK, Kowalski SR, Plummer JL, Cousins MJ, Armstrong PJ: Fentanyl blood concentration-analgesic response relationship in the treatment of postoperative pain. Anesth Analg 1988; 67: 329-37

Possible Mechanism: Fentanyl Inhibits Na^+ Channels





The potency of opioids to inhibit Na+ channels correlate well with the lipophilicity. (buprenorphine>fentanyl>sufentanil> tramadol>morphine>remifentanil)

The blocking potency and the analgesic potency do not correlate. (sufentanil>fentanyl>remifentanil> Buprenorphine> morphine>tramadol)

Local Anesthetic-like Inhibition of Voltage-gated Na+ Channels by the Partial [mu]-opioid Receptor Agonist Buprenorphine.
Leffler, Andreas; Frank, Georg; Kistner, Katrin; Niedermirtl, Florian; Koppert, Wolfgang; Reeh, Peter; Nau, Carla

Anesthesiology. 116(6):1335-1346, June 2012.
DOI: 10.1097/ALN.0b013e3182557917

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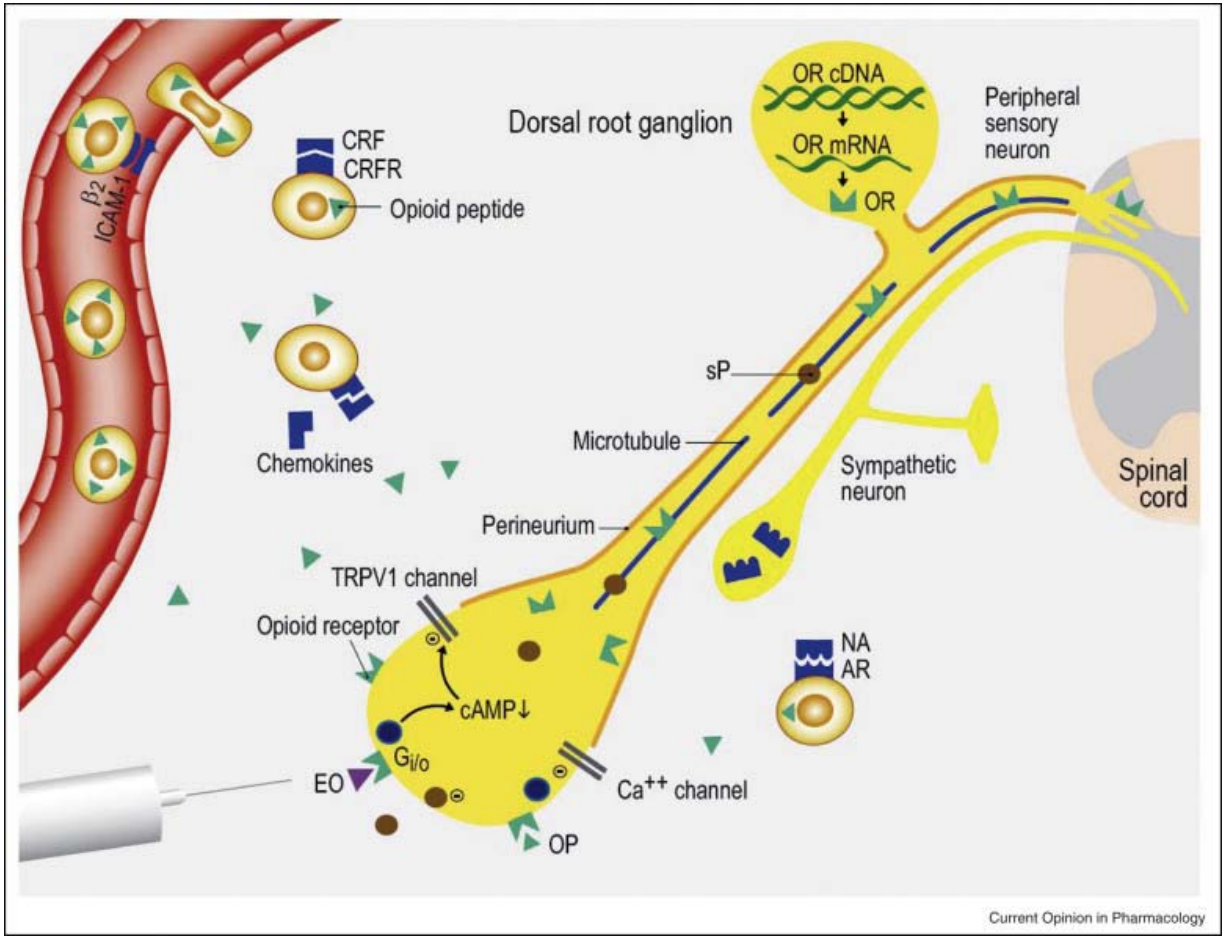
A detailed model of opioid pathways outside the central nervous system



Christoph Stein, Leonie Julia Lang, Peripheral mechanisms of opioid analgesia, Current Opinion in Pharmacology, Volume 9, Issue 1, February 2009, Pages 3-8

Conclusions

- Continuous fentanyl administration via a FNS catheter provided effective analgesia at significantly lower plasma levels compared to continuous IV infusions of fentanyl
- The analgesic effect found by the infusion of perineuronal fentanyl was superior to the administration of fentanyl into systemic circulation while the patient was ambulating, but similar when the patient was at rest
- The average serum fentanyl concentration at 24 hours post-TKR was 50% lower when administered perineuronally compared to systemic administration and was 50% lower than the minimal effective analgesia concentration
- We postulate that femoral nerve sheath catheter infusions of fentanyl may have a localized analgesic effect rather than systemic since serum levels were significantly lower

References

1. Stein C: Peripheral mechanisms of opioid analgesia. Anesth Analg 1993; 76: 182-91
2. Janson W, Stein C: Peripheral opioid analgesia. Curr Pharm Biotechnol 2003; 4: 270-4
3. Leffler A, Frank G, Kistner K, Niedermirtl F, Koppert W, Reeh P, Nau C: Local Anesthetic-like Inhibition of Voltage-gated Na+ Channels by the Partial [mu]-opioid Receptor Agonist Buprenorphine. Anesthesiology. 116(6):1335-1346, June 2012
4. Gourlay GK, Kowalski SR, Plummer JL, Cousins MJ, Armstrong PJ: Fentanyl blood concentration-analgesic response relationship in the treatment of postoperative pain. Anesth Analg 1988; 67: 329-37
5. Christoph Stein, Leonie Julia Lang, Peripheral mechanisms of opioid analgesia, Current Opinion in Pharmacology, Volume 9, Issue 1, February 2009, Pages 3-8

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