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THE SAFETY OF PERIOPERATIVE ESOMOL: A SYSTEMATIC REVIEW AND METAANALYSIS OF RANDOMIZED CONTROLLED TRIALS


Abstract

Purpose This Meta-Analysis attempted to review a significant number of prospective, randomized, placebo controlled trials to assess the overall safety and efficacy of esmolol in non-cardiac surgery. The purpose of this review was to synthesize current data into useful information for the anesthesia practitioner regarding the use of β₁ selective adrenergic blocking agents in populations at-risk for perioperative myocardial ischemia.

Methodology The researchers looked at randomized, placebo-controlled trials pertaining to the use of esmolol in patients undergoing non-cardiac surgery. They focused on the safety of various infused doses of esmolol, comparing bradycardia and hypotension in that group against a placebo group. Studies were excluded if they involved the use of other vasoactive medications. Cardio-protective usefulness of esmolol was assessed by reviewing the incidence of perioperative ischemia or MI in comparison to control groups. Extracted data was reviewed and categorized based on demographic information, study quality, drug doses, and method of administration. Because many studies were conducted differently, the authors used the random effects model as their default pooling strategy.

Result The search resulted in 67 randomized, placebo-controlled trials that met the authors’ criteria. Trials could be broken down into groups. Those studies looking at esmolol for controlled hypotension or treatment of existing perioperative hypotension were not used. Since the author’s goal was to analyze the safety of esmolol in non-cardiac surgical patients, they focused on studies pertaining to the prophylactic
use of esmolol to prevent unwanted perioperative
tachycardia and/or hypertension. Hypotension was
noted more often in studies that used bolus protocols
over those that used infusion protocols. Unplanned
hypotension was greatest in studies that used a fixed
dosing protocol.
It was impossible to determine whether or not the
incidence of perioperative MI or stroke was affected
due to the rare occurrence of these morbidities in the
studies analyzed. Few studies actually discussed
unexpected or undesired side effects. Esmolol was
shown to decrease the magnitude of perioperative
ischemia in comparison to placebo in multiple studies
of patients at risk.

Conclusion  The authors found a direct link
between the use of esmolol and perioperative
hypotension. Lowering bolus doses and starting
infusions at the low end of the therapeutic range
(50-300 mcg/kg/min) and titrated to the desired end-
point directly correlated with a reduction in
unexpected hypotension. Esmolol has been shown to
decrease both heart rate and blood pressure in a dose
dependent manner. It was shown that when titrated
effectively, esmolol decreased the incidence of
perioperative myocardial ischemia. It is therefore
generally accepted that esmolol is safe and effective in
decreasing the likelihood of postoperative cardiac-
related morbidity and mortality.

Comment
This was a very interesting article. The authors
managed to mesh the currently available data into a
concise and useable format. There is an overall
consensus that the current literature is accurate in
describing the usefulness and efficacy of perioperative
esmolol in preventing tachycardia and hypertension.
In reviewing other analyses, there is a lack of such a
resounding endorsement. β-blockade may actually
aggravate hypotension, has never been shown to
consistently or reliably control heart rate, and may
actually interfere with adequate cardiac output during
surgically challenging events (such as active bleeding,
anemia, or shock).1

The use of routine β-blockade will remain
controversial. One consensus is that controlling heart
rate is a primary mechanism for decreasing
myocardial oxygen demand and risk for perioperative
ischemia. Considering the available literature, there is
a convincing argument for the use of esmolol
selectively in patients that are at risk for perioperative
myocardial events. Episodic use is preferred over
routine planned prophylactic use. More studies need
to be done to determine the place of β-blockade in
the prevention of postoperative cardiac morbidity and
mortality.

Gerard Hogan, DNSc., CRNA

1. Landesberg G, Beattie WS, Mosseri M, Jaffe AS,
Alpert JS. Perioperative myocardial infarction.
Circulation 2009;119:2936-44.
Also of Interest:
Mangano DT. Perioperative cardiac morbidity.
Anesthesiology 1990;72:154-84.
Intraoperative Methadone Improves Postoperative Pain Control in Patients Undergoing Complex Spine Surgery

Anesth Analg 2011;112:218-23
Gottschalk A, Durieux ME, Nemergut EC

Abstract

Purpose The purpose of this study was to determine if a single bolus dose of methadone 0.2 mg/kg before incision for complex thoraco-lumbar spine surgery in adults improves pain control. A secondary purpose was to assess methadone side effects in this setting.

Background Severe postoperative pain is common after major spine surgery. Total intravenous anesthesia with propofol and sufentanil is commonly used to maintain anesthesia in these cases when neurophysiologic monitoring is used. Methadone is a long-acting opioid frequently administered to those with chronic pain. It is an opioid receptor agonist and NMDA receptor noncompetitive antagonist with a mean elimination half-life of 22 hours (range 15-60 hours), which may be beneficial after major spine surgery. Methadone has been limited in its use in the surgical setting as it has great potential to cause unwanted post-operative side effects which include prolonged sedation, respiratory depression, nausea, and vomiting. However, this patient population typically requires large doses of opioids for an extended period of time following surgery. Some researchers suggest that methadone, with its long duration of action, may be an alternative to sufentanil.

Methodology This was a prospective, randomized, single blind investigation of 30 patients, aged 18-75 years old, scheduled for elective multilevel thoracolumbar spine surgery with instrumentation and fusion. Exclusion criteria included preoperative methadone use, morbid obesity (BMI >36 kg/m²), history of substance abuse, history of myocardial infarction or heart failure, chronic renal failure, or liver failure or cirrhosis. Patients were randomized into one of two groups:

- Sufentanil Group: received 0.75 µg/kg initial loading dose of sufentanil before surgical incision followed by sufentanil infusion of 0.25 µg/kg/h
- Methadone Group: received 0.2 mg/kg subsequent to intubation

Anesthesia was maintained with propofol 50-150 µg/kg/min.; no potent inhalation agent was used. Inadequate intraoperative anesthesia (i.e., hypertension, tachycardia, patient movement) was treated with a bolus of 0.1 µg/kg of sufentanil every 2.5 minutes at the discretion of the anesthesia provider. When surgical wound closure was begun, the sufentanil was turned off and the patient extubated in the operating room or intensive care unit. Patients who remained intubated postoperatively...
did not receive any opioids as part of their sedation. All patients received postoperative PCA with either fentanyl, hydromorphone, or morphine. Postoperative analgesia was managed by the neurosurgeon.

All opioids were recorded as morphine equivalents. The following parameters were measured:

- Pain rating via visual analogue scale
- Preoperative opioid consumption (in morphine equivalents)
- Time after surgery to first pain medication
- Cumulative opioid requirement at 24, 48 and 72 hours postoperatively (in morphine equivalents)
- Complications defined as:
  - hypotension (MAP < 50 mm Hg)
  - need for vasopressors
  - incidence of respiratory depression
  - respiratory arrest
  - need for naloxone
- The incidence of hypoxemia or desaturation or the need for supplemental oxygen
- The incidence of cardiac arrhythmias, MI, PONV and any treatment that was given

Student t tests or Mann-Whitney U tests were used to make group comparisons. Results are presented as the mean ± SD or median (25-75% interquartile range). A P < 0.05 was considered significant.

**Result**  A total of n= 29 subjects (methadone n = 13; sufentanil n = 16 completed the study). The mean age in the methadone group was 62.9 ± 9.5 as compared to 53.1 ± 15 in the sufentanil group (P = 0.051).

There were no differences in BMI (methadone group: 26.3 ± 4.6 vs. sufentanil 28.1 ± 4.7; P = 0.323), male gender (methadone group: 45.5% vs. sufentanil group 36.5%; P = 0.466), and ASA status (P = 0.448).

Median preoperative opioid consumption (morphine equivalents) was 8.0 (0-16) mg in the methadone group as compared to 7.5 (0-21.6) mg in the sufentanil group (P = 0.771). Median surgical duration was 285 (248-467) minutes in the methadone group and 329 (283-475) minutes in the sufentanil group (P = 0.313).

Median time to extubation was similar between the two groups (methadone group: 15 (13.5-18.25) minutes vs. sufentanil group 11.5 (5-33) minutes, P = 0.58).

The time from the end of surgery to first request of pain medications was longer in the methadone group; however, the difference was not statistically significant. The methadone group had significantly less pain at 48 hours compared to the sufentanil group (Figure 1; P < 0.05). However pain scores were similar at 24 and 72 hours (P = NS). Median opioid consumption at 24, 48 and 72 h was over twice as great in the sufentanil group when compared to the methadone group at each time point. However, the difference was only significant at 48 and 72 hours (Table 1). There was no significant difference in side effects between the two groups. No serious complications occurred in either group.

### Table 1. Postoperative opioid consumption

<table>
<thead>
<tr>
<th>Time</th>
<th>Methadone group n = 13</th>
<th>Sufentanil group n = 16</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h</td>
<td>50 (5, 390)</td>
<td>110 (10, 455)</td>
<td>ns</td>
</tr>
<tr>
<td>48 h</td>
<td>25 (5, 175)</td>
<td>63 (10, 230)</td>
<td>0.023</td>
</tr>
<tr>
<td>72 h</td>
<td>15 (0,80)</td>
<td>34 (10, 195)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Note. Results are median (min, max) morphine equivalents in mg.
Conclusion  Postoperative pain control after a single 0.2 mg/kg pre-induction bolus of methadone improves pain control significantly at 48 hours postoperatively. Additionally, methadone reduced opioid requirements significantly at 48 hours and 72 hours postoperatively. Reported side effects and/or complications (which were minimal in both groups) of those who received methadone were no different in quantity compared to those who received sufentanil.

Methadone has a median half-life of 22 hours, however there is significant variability in metabolism rates among individuals. The investigators hypothesized they would see differences in opioid consumption at 24 hours given methadone’s half-life. The sufentanil group consumed twice as much opioid at all time points, however the difference was only statistically significant at 48 and 72 hours. The authors suggested in their discussion this finding of significantly less opioid consumption at 48 and 72 hours, which is long past the median-half life of methadone, may be due to methadone’s ability to attenuate opioid tolerance and hyperalgesia. This theory is speculative, and this difference at 24 hours may be because the study was underpowered. If they would have had a larger sample size they may have seen differences at all time points.

Editors Note: Both Dr. Spence and Dr. Golinski analyzed and commented upon this article. Dr. Golinski’s comments follow in two pages.

Dr. Spence’s Comments

Multilevel thoracolumbar spine surgery with instrumentation and fusion is associated with significant postoperative pain. Furthermore, many of these patients may present with a history of chronic back pain which may increase their postoperative opioid requirements. In this study the investigators demonstrated that a single preoperative dose of methadone resulted in significantly less pain at 48 hours, and significantly less opioid requirements at 48 and 72 hours. These results are not surprising given the long duration of action of methadone.
There were some weaknesses to this study. Patients in the methadone group were almost 10 years older than those in the sufentanil group. However, it may be clinically relevant as older patients may require less opioids, and may have lower methadone metabolism, which may explain the difference. With a larger sample size the groups may have been statistically different with respect to age. Therefore, this age difference could partially explain the differences seen. Additionally, the investigators do not describe the number of levels fused or the specific procedures performed for each group. This would have helped in the interpretation of their results. The investigators did not report if the patients were taking any adjunct pain medications (i.e., gabapentin, NSAIDS) preoperatively or postoperatively. Patients also received different types of PCA opioid agents (i.e., fentanyl, hydromorphone and morphine), and it is not known if a basal rate was used in either group, which may have influenced the results. Finally, the investigators used t-tests to compare pain and opioid consumption for each of the three days analyzed. A more appropriate analysis would have been to use a repeated measures analysis of variance or a nonparametric equivalent and used a more conservative P value to be considered significant (i.e., P <0.01) since they were making multiple comparisons.

Given these limitations, results of this study should be considered preliminary. If anesthesia providers choose to use methadone they need to ensure that the surgeons and nurses know the patient received a long acting opioid and that they should avoid or cautiously prescribe other sedatives and hypnotics. If a PCA is ordered I would not recommend a basal rate.

Anesthesia providers may want to consider having an anesthesia “pain service” manage these patients to minimize the risks. Finally, as continuous end-tidal carbon dioxide becomes more readily available, patients administered long acting opioids might benefit from this monitor.

Dennis Spence, PhD, CRNA

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.

**Dr. Golinski’s Comments**

Typically, those who have extensive spine surgeries present with significant pain prior to surgery, and are very uncomfortable following their surgical procedure. Their pain scores can be very high. Many of these patients experience hyperalgesia phenomenon. Providing the proper level of analgesia is an extremely complicated process and while it may be possible to totally alleviate pain with large doses of narcotics, it is these large doses which cause numerous complications, some of which can be lethal.

Numerous case studies have reported post-operative respiratory depression and respiratory arrest in these patients, typically the result of trying to manage pain with high doses of narcotics. With such large doses of narcotics, it may be impossible to eliminate these side
effects, even when preventative drugs are given. Leaving a patient intubated, ventilated and narcotized due to the inability to manage pain seems antiquated and barbaric yet so does emerging a patient and denying pain medication because of the potential complications. There has to be a better way. Here enters methadone, a drug with some unique properties. Methadone can attenuate or even prevent opioid tolerance and it has a long duration of action. These traits are beneficial in this specific patient population.

The results of this study were surprising; patients who received methadone derived the greatest benefit between 48 and 72 hours postoperatively - not in the initial 24 hours postoperatively. The investigators had a meaningful response to this: Is the primary advantage of methadone not in its ability to provide analgesia, but rather in its ability to attenuate opioid tolerance and hyperalgesia?

Mary A. Golinski, PhD, CRNA

**Hyperalgesia**- A greater than normal sensitivity to painful stimuli.

**Analgesia Tolerance**- The phenomenon whereby chronic exposure to a drug diminishes its antinociceptive or analgesic effect, or creates the need for a higher dose to maintain this effect. The tolerant person is less susceptible to the pharmacologic effects of a drug as a consequence of its prior administration.
THE EFFECTS OF PREOPERATIVE INTRAVENOUS ACETAMINOPHEN IN PATIENTS UNDERGOING ABDOMINAL HYSTERECTOMY

Abstract

Purpose The purpose of this study was to determine the post-operative analgesic efficacy of intravenous acetaminophen, when administered prior to incision, in females undergoing total abdominal hysterectomy.

Background The mechanisms involved in the post-operative pain response suggest that a multimodal approach may be efficacious by enhancing the quality of analgesia and diminishing the untoward effects of opioids. Non-steroidal anti-inflammatory drugs (NSAIDS), when co-administered with morphine, have been shown to reduce the side effects of morphine alone, however, there are contraindications that exist related to NSAIDS and many patients cannot take them. Acetaminophen has very few contraindications and is relatively free from side effects at therapeutic clinical doses. Very little is known about the pre-emptive effects of acetaminophen and how it may modulate post-operative pain when administered in combination with an opioid.

Methodology This research was carried out as a placebo-controlled, double blind, randomized study. A total of 76 women scheduled for elective abdominal hysterectomy under general anesthesia were randomized into one of two groups. Prior to the induction of anesthesia, the acetaminophen group received 2 grams of acetaminophen intravenously while the placebo group received normal saline in equal volume as the study drug. The anesthetic was standardized for all subjects and all operations were performed using the same incision type.

Thirty minutes prior to conclusion of surgery, 7 mg hydromorphone was administered to subjects in both groups. At the conclusion of the procedure, each subject was given a PCA device set to deliver 0.2 mg bolus of hydromorphone with a specified lock out interval. If subjects needed additional analgesia during the study period, ketorolac (Torodol) 30 mg intravenously was given; no other analgesics were used at any time period during the study. The primary outcome variable measured was PCA hydromorphone consumption for 24 hours post-operatively. The secondary outcome variables measured included pain scores via a VAS, both at rest and during activity, and any side effects, for 24 hours post-operatively.

Result A total of 71 patients were included in the study. There were no statistical differences in the demographic data between the groups. The following outcome variables were found to be significant:
• Total 24 hour hydromorphone consumption was lower in the acetaminophen group
• Overall hydromorphone consumption was reduced at all time points (1, 2, 6, 12, & 24 hours) \((P = 0.013)\)
• The incidence of PONV was lower in the acetaminophen group \((P = 0.044)\)

**Conclusion**  The pre-operative administration of IV acetaminophen reduced hydromorphone consumption in patients undergoing abdominal hysterectomy as well as reduced the incidence of post-operative nausea and vomiting. The VAS scores for pain during rest and activity were similar in both groups; the number of patients needing ketorolac, however, did not differ. Sedation scores, a secondary outcome measure of untoward effects, were lower in the acetaminophen group (not statistically significant).

**Comment**  Multimodal analgesia is becoming the norm, and should be, as we learn more and more about pain, pain receptors and pathways, and the various side effects of drugs within multiple classes. Our goal, of course, is a safe (non respiratory depressed and/or overly sedated) and highly satisfied patient experiencing positive outcomes. Combining different drug classes (opioids) with non-opioids (Cox -2 inhibitors, NSAIDS) delivered through various routes and even including neuraxial use of local anesthetics are showing extremely favorable results. Patients are more satisfied and the untoward effect of each respective drug can often be minimized when multimodal pain therapy is used. With the multimodal approach you do not need high or escalating doses of any one agent. As a result, side effects related to each drug class are reduced.

Acute post-operative pain remains a challenge, however a multimodal therapeutic approach enhances the efficacy of pain-control. Intravenous acetaminophen appears to represent another class of medications with a place in multimodal analgesia.

Mary A. Golinski, PhD, CRNA

**Intravenous Acetaminophen (Ofirmev)** was approved by the FDA in November 2010. Its exact mechanism of action for acute pain management is unknown and is theorized to be related to several entities: inhibition of cyclooxygenase isoenzymes, interaction with the endogenous opioid pathway, activation of the serotonergic bulbospinal pathway, involvement of the nitric oxide pathway, and an increase in the cannabinoid/vanilloid tone. The package insert can be found at:  [http://www.ofirmev.com/](http://www.ofirmev.com/)
Abstract

Purpose  The purpose of this study was to compare the incidence of transient neurologic symptoms (TNS) with either levobupivacaine 5 mg/mL or lidocaine 20 mg/mL.

Background  Transient neurologic symptoms (TNS) were first described in 1993 in four patients who had undergone spinal anesthesia with hyperbaric 5% lidocaine. Reported symptoms of TNS include the presence of pain and/or dysesthesia in the buttocks, thighs, and/or lower limbs occurring after recovery from spinal anesthesia. Lidocaine has been most commonly associated with the development of TNS with a reported incidence of 0 to 40%, though TNS has been reported after other local anesthetics as well and even after general anesthesia without regional anesthesia. The concentration of glucose, baricity, and local anesthetic concentration does not increase the risk of TNS. The reported incidence of TNS after bupivacaine is less than lidocaine (incidence established by case reports not research). It is postulated that levobupivacaine would have a similar incidence to bupivacaine.

Methodology  This was a prospective, randomized, double-blind investigation of 60 ASA I and II patients, aged 20 to 80 years old scheduled to undergo minor orthopedic, varicose vein, inguinal hernia repair, or appendectomy. Patients were excluded if they had a history of acute or chronic back problems or severe deformity of the spine, previous back surgery, previous failed spinal anesthesia, or neurologic problems such as multiple sclerosis, spinal cord lesions, diabetes, obesity (BMI > 30 kg/m²), allergy to the study medication, or history of substance abuse. Patients were randomized to receive a spinal anesthetic consisting of 4 mL of either isobaric levobupivacaine 5 mg/mL or isobaric lidocaine 20 mg/mL. All spinal anesthetics were placed at the L2-3 or L3-4 interspace.

On postoperative days one through three patients were evaluated for TNS by a blinded investigator. Patients who experienced TNS symptoms were evaluated again at 1 week. Symptoms and severity of TNS was evaluated with a standardized checklist. TNS was defined as pain and/or dysesthesia in the area of the buttocks, thighs, calves, or feet after recovery of the spinal anesthetic. TNS pain severity was measured with a 0-10 verbal numeric rating scale (VNRS). The time from spinal block cessation to onset of TNS was recorded. Postoperative and TNS pain was treated with dexketoprofen trometamol 25 mg tablets twice a day.
The primary outcome of this study was the frequency of TNS. Descriptive and inferential statistics were used to analyze the results. A P <0.05 was considered significant.

**Result** A total of 60 subjects completed the study; 30 in each group. There were no significant differences between the two groups concerning baseline demographics and duration or type of surgery. The overall mean age of the sample was 30 years. In the levobupivacaine group (LB) 80% of the subjects were men compared to 76.6% in the lidocaine group (L). The majority of the surgical procedures were varicose vein stripping (LB = 56.6% vs. L: 53.3%), followed by inguinal hernia repair (LB = 20% vs. L = 23.3%), minor orthopedic (LB = 10% vs. L = 13.3%), and appendectomy (LB = 13.3% vs. L = 10%).

The incidence of TNS was significantly greater in the lidocaine group (26.6%, n = 8) compared to levobupivacaine group (3.3%, n = 1; P = 0.026; Figure 1). All TNS patients complained of bilateral symptoms, with most reporting the pain extended across multiple regions, including the buttocks, thighs, and lower legs. Pain severity in the lidocaine group ranged from 1/10 to 6/10 (median 3/10). The patient in the levobupivacaine group who experienced TNS had a varicocelectomy (pain score 6/10). He described the pain as radiating from his buttocks to his hips. The pain resolved within 72 hours. All patients with TNS symptoms reported NSAIDs relieved the pain.

**Conclusion**

The incidence of TNS was greater after lidocaine compared to levobupivacaine. However, TNS can occur after spinal anesthesia with levobupivacaine. TNS symptoms typically lasted less than 1 week.

![Figure 1. Comparison of TNS symptoms](image)

Note. In the lidocaine group 5 of 8 patients in the reported bilateral pain in the buttocks, thighs and calves; 2 of 8 complained of pain in the thighs; and 1 of 8 in the calves. In the levobupivacaine group, the 1 patient with TNS reported bilateral pain the buttocks and thighs.
Comment
This study further demonstrates that transient neurological symptoms are more common after lidocaine. However, they can also occur after spinal anesthesia with other local anesthetics. The symptoms typically resolve in less than 1 week, although in this study it is difficult to determine exactly when the symptoms resolved. The study could have been strengthened if the investigators had reported the time until resolution of TNS in the lidocaine group. However, the short duration of the symptoms is reassuring.

I think if I had a patient who developed TNS after a spinal anesthetic, I would inform them that the symptoms should resolve within a week and that they could take NSAIDS or postoperative pain medications as needed to alleviate the pain.

A limitation of this study is its small sample size and inclusion of multiple surgical populations. The investigators do not describe what surgeries the patients who experienced TNS in the lidocaine group had or their ages. The study would have been stronger if they had enrolled a more homogenous population (i.e., patients undergoing hernia repair).

Dennis Spence, PhD, CRNA

Editor’s Note: dexketoprofen trometamol is an NSAID available in the United Kingdom, but not in the USA.

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.
Spinal anaesthesia for ambulatory arthroscopic surgery of the knee: A comparison of low-dose prilocaine and fentanyl with bupivacaine and fentanyl

Br J Anaesth 2011;106:183-8
Black AS, Newcombe GN, Plummer JL, McLeod DH, Martin DK

Abstract

Purpose The purpose of this study was to compare the behavior and characteristics of subarachnoid block with low-dose prilocaine with fentanyl or bupivacaine with fentanyl.

Background Meta-analyses suggest that spinal anesthesia results in reduced postoperative pain and analgesic requirements after ambulatory surgery when compared to general anesthesia. The problem with spinal anesthesia is that traditional doses prolong recovery after ambulatory surgery. To address this issue investigators have evaluated various techniques and agents for “low-dose” spinal anesthesia. These techniques involve the use of smaller doses of local anesthetics in combination with fentanyl. The addition of fentanyl has been demonstrated to increase the sensory block without increasing motor block or time to micturition. Bupivacaine is the most common spinal anesthetic; however it is associated with prolonged blockade. Lidocaine has a better recovery profile; however it is associated with transient neurologic symptoms (TNS). Prilocaine has a similar potency and duration of action as lidocaine and has a lower reported incidence of TNS. However there are limited studies evaluating a low-dose combination of prilocaine with fentanyl for knee arthroscopy.

Methodology This prospective, randomized, double-blind investigation included 50 ASA I-III patients scheduled for knee arthroscopy under spinal anesthesia. Exclusion criteria included contraindications to spinal anesthesia or allergies to study medications. Patients were randomized to receive a spinal anesthetic consisting of either plain bupivacaine (Bupiv) 7.5 mg with fentanyl 20 mcg or prilocaine (Pri) 20 mg with fentanyl 20 mcg. Spinal anesthetics were prepared by the pharmacy to a total volume of 2 mL. The anesthetist added fentanyl 20 mcg (0.4 mL) prior to injection of the spinal anesthetic. All spinal blocks were performed in the sitting position at the L3-4 or L4-5 interspace. Midazolam was titrated for sedation and IV fentanyl was administered for pain. If sedation and analgesia were inadequate, general anesthesia was administered.

The primary outcome was sensory block regression (evaluated with ice) to an L-4 level. Secondary outcomes included highest attained sensory dermatome level, onset time for highest sensory level, motor block regression as measured by a Bromage scale at 1 and 2 hours, time to micturition, hemodynamic changes, incidence of pruritus, comfort scores, and satisfaction scores. A power analysis determined 23 subjects were needed in each group.
Descriptive and inferential statistics were used to analyze the results. A $P$ value $<0.05$ was considered significant.

**Result** A total of 49 subjects were enrolled in the study. Due to pharmacy error 26 syringes of bupivacaine and 23 syringes of prilocaine were prepared. Two patients in the prilocaine group required general anesthesia. One patient had a failed spinal anesthetic due to poor CSF flow; therefore this patient was excluded from analysis. The second patient requested general anesthesia after placement of the spinal anesthesia because the operating room temperature was too high because of air-conditioning failure after start of the procedure. This latter patient’s data was included in the postoperative analysis.

The mean age was 50 years and the weight 82 kg in both groups. The median time from spinal injection to arrival in the recovery room was 35 min (range 20-55 min). The median highest block height was T-3 (range: C4-T10) in the bupivacaine group and T-4 (range: C4-T8) in the prilocaine group ($P = 0.056$). Median onset time to the highest sensory level was significantly shorter in the prilocaine group compared to the bupivacaine group ($Bupiv = 20$ min, range 7.5-60 min vs $Pri = 11.3$ min, range 2.5-55 min; $P < 0.001$). The median time for regression to an L-4 level was significantly shorter in the prilocaine group ($Pri = 97$ min, 95% CI, 90-115 vs. $Bupiv = 280$ min, 95% CI, 207-not computable; $P < 0.001$; Figure 1). Five (22%) patients in the prilocaine group never had an appreciable motor block. Degree of motor block was significantly less at 1 hour, with 75% of patients in the prilocaine group having no motor block compared to 0% of patients in the bupivacaine group ($P <0.001$).

At 2 hours, 86% of patients in the prilocaine group had no motor block compared to 27% in the bupivacaine group ($P < 0.001$).

Median time to micturition occurred significantly faster in the prilocaine group ($Pri = 205$ min, 95% CI, 185-220 vs. $Bupiv = 275$ min, 95% CI, 250-300; $P < 0.001$). Significantly more subjects in the bupivacaine group had a clinically significant decrease in systolic blood pressure $>20\%$ when compared to the prilocaine group ($Bupiv = 73\%$ vs. $Pri = 32\%$, $P = 0.004$). Incidence of pruritus was similar between the groups ($P = 0.20$). Comfort and satisfaction scores were similar between the two groups. No patient reported TNS.

**Conclusion**
Low-dose prilocaine (20 mg) with fentanyl (20 mcg) was a better choice for outpatient knee arthroscopy when compared to low-dose plain bupivacaine (7.5 mg) with fentanyl (20 mcg) because it provided faster block resolution, decreased time to urination, and earlier patient discharge.

**Comment**
In this study, the investigators found that 20 mg of prilocaine with 20 mcg fentanyl provided adequate anesthesia with a shorter block duration when compared to 7.5 mg plain bupivacaine with 20 mcg fentanyl. It is important to point out that this dose of prilocaine is the lowest dose reported in the literature.
for knee arthroscopy and is probably not suitable for procedures lasting longer than 45 minutes. Additionally, 20 mg of prilocaine is associated with less motor blockade when compared to 7.5 mg plain bupivacaine. It would be important to counsel the patient that they may not have complete motor block with this dose of prilocaine. Likewise, it would be important to verify with the surgeon that minimal motor block is appropriate for the surgery. In my experience, diagnostic knee arthroscopies can be performed with low-dose spinal anesthetics, however, if significant ligament repairs or prolonged surgical times are anticipated a larger dose may be required.

If we compare the results of this study to those reported in another levobupivacaine study recently included in Anesthesia Abstracts (see January 2011 issue), one can see that this dose of prilocaine resulted in a shorter block duration. Sensory block recovery time with this dose is slightly faster than that reported for levobupivacaine 4 mg with fentanyl 10 mcg. In this study the median time was 97 minutes to recede to a L-4 level with this dosage of prilocaine when compared to 90 minutes for levobupivacaine to achieve an L-2 level. I suspect the degree of motor block was slightly greater for 4 mg levobupivacaine when compared to 20 mg prilocaine with fentanyl 10-20 mcg. This information is useful for anesthesia providers because it allows them to compare clinical effectiveness and anticipated duration of action of these two techniques.

Time to micturition was shorter in the prilocaine group, however it was still greater than 3 hours. Urinary retention is the most common side effect with spinal anesthesia, and it may contribute to delayed discharge. It is important to counsel patients on this side effect and to consider your institutions policy on

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**Figure 1. Median times for regression of sensory block to L-4**

<table>
<thead>
<tr>
<th>Time in minutes</th>
<th>Prilocaine (20 mg)</th>
<th>Bupivacaine (7.5 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>* Prilocaine</td>
<td>Bupivacaine</td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* P < 0.001

**Note.** Values are median. All patients received fentanyl 20 mcg added to spinal anesthetic. Total volume 2.4 mL. Prilocaine group (median time = 97 min, 95% CI, 90-115) vs. Bupivacaine group (median time = 280 min, 95% CI, 207-not computable).
urination prior to discharge. If patients are required to urinate prior to discharge this may limit the benefit achieved with low-dose spinal anesthesia.

There were a few limitations to this study. The investigators did not present the specific gravity of these agents, however they did report that hyperbaric prilocaine was not available. In this study the investigators used plain (isobaric) bupivacaine and prilocaine. I suspect the baricity was reduced with the addition of the fentanyl and dilution by the pharmacy. Therefore I suspect both agents may have been slightly hypobaric. Peak block height was C-4 in both groups which supports this theory. The hypobaric baricity may also have contributed to the higher incidence of hypotension with these small doses. Finally, the investigators did not report the height of the patients which may have influenced the block height, nor did they report total fluids administered.

Dennis Spence, PhD, CRNA


The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.
Comparison between ultrasound-guided transverse abdominis plane and conventional ilioinguinal/iliohypogastric nerve blocks for day-case open inguinal hernia repair

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Aveline C, Le Hetet H, Le Roux A, Cognot F, Vinet E, Tison C, Bonnet F

Abstract
Purpose The purpose of this study was to compare the efficacy of ultrasound-guided transverse abdominis plane (TAP) block with ilioinguinal/iliohypogastric nerve block (INH) on acute and chronic postoperative pain after inguinal hernia repair.

Background Ilioinguinal/iliohypogastric nerve blocks are commonly performed to provide postoperative analgesia after open inguinal hernia repair. Recently the ultrasound-guided TAP block has been described as providing effective analgesia after lower abdominal surgery. However, there are no studies to date which have compared INH with TAP blocks in patients undergoing open inguinal hernia repair.

Methodology This was a randomized, single blind study of 273 patients undergoing open inguinal hernia repair with mesh under general anesthesia. Patients were randomized to receive either an ultrasound-guided TAP or INH nerve block with 0.5% levobupivacaine (1.5 mg/kg). Patients were blinded to the block technique. Thirty minutes after the block, general anesthesia was induced with propofol and sufentanil and the airway maintained with a laryngeal mask airway. Sevoflurane 0.8-1% with a 50% mixture of air and oxygen was used for maintenance. All patients received paracetamol 1 gm and ketoprofen 100 mg IV with droperidol 1.25 mg after induction. The same two surgeons performed all surgeries. In the PACU 3 mg morphine was titrated as needed to achieve a visual analogue scale (VAS; 0-100 mm) pain scores ≤ 30 mm. After discharge from the PACU, patients received paracetamol 1 gm every 6 h and ketoprofen 150 mg every 12 h. Rescue analgesia was immediate release morphine tablets (20 mg).

Patients were discharged home when their pain scores were ≤ 40 mm during coughing and they were without PONV.

Outcomes included pain scores at rest and with movement before discharge from the PACU, 4 and 12 hours after surgery, on postoperative day (POD) 1 and 2, and again at 3 and 6 months. Neuropathic pain was evaluated at 6 months with the DN4 questionnaire. A score ≥ 4 on the DN4 indicates a high probability of neuropathic pain. Secondary outcomes included oral morphine requirements, PONV incidence, and sleep quality. All outcomes were evaluated by an investigator blinded to treatment group.
Sample size calculations determined 130 subjects per group would be needed to find a 40% difference in VAS pain scores ≥ 40 mm with movement at 6 months. Sample size was increased to 275 to account for attrition. Descriptive and inferential statistics were used to analyze the results. A P < 0.05 was considered significant.

**Result** No significant differences were noted in demographic variables, baseline pain scores, surgical duration, or intraoperative sufentanil requirements between the two groups. Median VAS pain scores at rest were significantly lower in the TAP group at 4 h (P = 0.04), 12 h (P = 0.0014), and 24 h (P = 0.013; Figure 1). Pain scores at rest and with movement at 48 h, and at 3 and 6 months were similar between the two groups (P > 0.05). Median postoperative morphine requirements were significantly less in the TAP group at 24 h (3 tablets vs. 4 tablets; P =0.03). No complications occurred with either block. One patient in the INH group required overnight admission due to quadriceps weakness secondary to local anesthetic extension to the femoral nerve.

Neuropathic pain scores were similar at 3 and 6 months. At 6 months 13.6% of patients in the TAP group and 15.7% of patients in the INH group had DN4 scores ≥ 4, indicating they had probable neuropathic pain. At 6 months the proportion of patients with VAS pain scores ≥ 40 mm with movement at 48 h, and at 3 and 6 months were similar between the two groups (P > 0.05). Median postoperative morphine requirements were significantly less in the TAP group at 24 h (3 tablets vs. 4 tablets; P =0.03). No complications occurred with either block. One patient in the INH group required overnight admission due to quadriceps weakness secondary to local anesthetic extension to the femoral nerve.

**Figure 1. Comparison of Median VAS Pain Scores**

Note. TAP = transverse abdominis plane block. INH = ilioinguinal/iliohypogastric nerve block.
movement was similar between the two groups (TAP: 18.2%, vs. INH: 22.4%; P = 0.8). Six patients (4.5%) in the TAP group reported pain interfered with their daily activities compared to 9 (6.7%) patients in the INH group (P = 0.45).

**Conclusion** Postoperative pain and analgesic requirements within the first 24 hours were significantly better in patients who received a TAP block when compared to an INH block for inguinal hernia repair. Neither block prevented the development of chronic pain.

**Comment**
Inguinal hernia repair is associated with significant acute and chronic pain.\(^1,2\) Chronic pain may be neuropathic or nocioceptive in origin. Neuropathic pain can result from damage to the ilioinguinal, iliohypogastric or genital branch of the genitofemoral and lateral femoral cutaneous nerve, respectively. Nocioceptive pain on the other hand may result from damage to the pubic tubercle during stapling of the mesh or from trauma to deep muscle layers during inguinal hernia repair. Damage to the nerves or tissue may lead to peripheral and central sensitization, resulting in permanent alterations in CNS pain perception. This can result in chronic pain which is unresponsive to traditional analgesics.

In this study the investigators found a TAP block provided better acute postoperative pain control when compared to the “blind” INH block. However, they found no difference in the incidence or severity of chronic pain. Approximately 20% of patients in both groups reported chronic pain at 6 months, with 5.6% of patients reporting the pain interfered with their daily lives. These results are consistent with what is reported in the literature.\(^1,2\) Given the complex nature of chronic pain after inguinal hernia repair, it is not surprising that neither block reduced the incidence of this outcome. Certainly further research is needed to explore methods for decreasing chronic pain after inguinal hernia repair.

Ultrasound-guided TAP blocks are more effective than INH blocks because the provider can see where the local anesthetic is being injected. This explains why the TAP block is more effective than INH blocks in providing postoperative pain relief after inguinal hernia repair. An additional advantage is that a continuous TAP catheter can be placed and the patient discharged home with a continuous perineural infusion of local anesthetic for several days.\(^3\) The problem with TAP blocks are they take a long time to set up (20-30 minutes) so general or spinal anesthesia may be required for the procedure if there is not enough “soak time.” Additionally, the block requires ultrasound equipment with a provider experienced with ultrasound-guided peripheral nerve blocks. In this article the authors provide an excellent description and figures demonstrating the TAP block. I recommend if anesthesia providers are interested in learning how to perform a TAP block they should work alongside an experienced regionalist and review this article and other books on ultrasound-guided peripheral nerve blocks.

Dennis Spence, PhD, CRNA


**Editors Note:** Paracetamol is a European formulation of acetaminophen (Tylenol). Ketoprofen is an NSAID sold under the trade name Orudis in the USA.

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.