

Tramadol as adjunct to psoas compartment block with levobupivacaine 0.5%: a randomized double-blinded study[†]

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Background. Tramadol has been administered peripherally to prolong analgesia after brachial plexus and neuraxial blocks. Our aim was to evaluate the systemic and perineural effects of tramadol as an analgesic adjunct to psoas compartment block (PCB) with levobupivacaine.

Methods. In a randomized, prospective, double-blinded trial, 60 patients (ASA I–III), aged 49–88 yr, undergoing primary total hip or knee arthroplasty underwent PCB and subsequent bupivacaine spinal anaesthesia. Patients were randomized into three groups. Each patient received PCB with levobupivacaine 0.5%, 0.4 ml kg⁻¹. The control group (group L, n=21) received i.v. saline, the systemic tramadol group (group IT, n=19) received i.v. tramadol 1.5 mg kg⁻¹ and the perineural tramadol group (group T, n=20) received i.v. saline and PCB with tramadol 1.5 mg kg⁻¹. Postoperatively patients received regular paracetamol 6-hourly and diclofenac sodium 12-hourly. Time to first morphine analgesia, 24-hour morphine consumption, sensory block, pain and sedation scores and haemodynamic parameters were recorded.

Results. Time (h) to first morphine analgesia was similar in the three groups [mean (SD)]: group L, 11.2 (6.6); group T, 14.5 (8.0); group IT, 14.6 (6.8); *P*=0.35. Twenty-four-hour cumulative morphine (mg) consumption was also similar in the three groups [group L, 21.9 (10.1); group T, 19.8 (6.7), group IT, 16.5 (9.5)], as were durations of sensory and motor block. There were no differences in the incidence of adverse effects except that patients in group IT were more sedated at 14 h than group L (*P*=0.02).

Conclusion. We conclude that our data do not support a clinically important local anaesthetic or peripheral analgesic effect of tramadol as adjunct to PCB with levobupivacaine 0.5%.

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Clonidine and other adjunctive agents are commonly administered to prolong regional blocks.¹ Although clonidine successfully prolongs brachial plexus block,² concerns regarding its adverse haemodynamic³ and sedative effects⁴ have prompted investigators to examine alternative adjuncts for regional anaesthesia.

Tramadol is an analgesic drug, acting at central and peripheral μ -opioid and monoaminergic receptors.⁵ Tramadol also exhibits local anaesthetic properties.⁶ A study investigating the effects of tramadol 100 mg, sufentanil 20 μ g and clonidine 1.5 μ g kg⁻¹, combined with ropivacaine 0.75%, demonstrated that each adjunct similarly prolonged analgesia and anaesthesia of brachial plexus block, but that the incidence of adverse effects was less in the tramadol than clonidine group.⁴

The use of tramadol as an adjunct for brachial plexus block is supported by two further studies.^{7,8} However, its use in other regional block settings has produced less consistent results.^{9,10}

The use of adjunctive tramadol has not been investigated in the setting of the psoas compartment block (PCB). Despite clonidine's beneficial effects in brachial plexus blockade, we have recently shown that perineural clonidine (1 μ g kg⁻¹) does not prolong the action of levobupivacaine 0.5% in PCB.¹¹

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The aims of our study were therefore (i) to determine if tramadol (1.5 mg kg^{-1}) prolongs analgesia after PCB with levobupivacaine 0.5% and (ii) to compare the analgesic effect of tramadol after i.v. administration compared with perineural administration with levobupivacaine.

Methods

After institutional ethical committee approval and having obtained written informed consent from each patient, 60 ASA physical status I–III patients, aged 49–88 yr, scheduled for either primary hip or knee arthroplasty were included in a prospective, double-blinded, randomized, controlled trial. Exclusion criteria were concurrent or chronic medication with tramadol, perioperative use of ondansetron and contraindications to regional anaesthesia or NSAIDs.

On arrival of the patient in the anaesthesia induction room, a 16–18 G i.v. cannula was inserted. Routine monitoring consisted of continuous electrocardiography, pulse oximetry and non-invasive blood pressure at 5-min intervals (AS 3; Datex Instrumentarium, Finland). Baseline blood pressure was recorded. Patients then received midazolam 2–5 mg i.v. before PCB and Hartmann's solution 10 ml kg^{-1} was rapidly administered. All patients underwent PCB with subsequent spinal anaesthesia.

Patients were randomly assigned to one of three groups according to randomization tables. The results were made available to investigators using sealed envelopes, one for each patient recruited. Patients in group L received levobupivacaine 0.5%, 0.4 ml kg^{-1} (Chirocaine®; Abbott Laboratories, Dublin, Ireland) for PCB and saline 0.9%, 5 ml i.v. Patients in group T received levobupivacaine 0.4 ml kg^{-1} , 0.5% in combination with tramadol 1.5 mg kg^{-1} (50 mg ml^{-1}) (Tradol®; Rowex, Bantry, Ireland) for PCB and saline 0.9%, 5 ml i.v. Patients in group IT received levobupivacaine 0.5%, 0.4 ml kg^{-1} for PCB and tramadol 1.5 mg kg^{-1} i.v. made up to 5 ml with saline 0.9%. The drug solutions to be administered were prepared by an anaesthetist not involved in block performance, patient care or data collection.

The same operator (SM) performed all PCBs. The patients were placed in the lateral position, operative side uppermost. The technique for PCB was as described by Capdevila and colleagues.¹² After identification of the skin point for needle insertion, lidocaine 1%, 3 ml was injected into the skin and subcutaneous tissues. The skin was prepared with chlorhexidine. A Stimuplex A® 100 mm needle (B. Braun Medical, Melsungen, Germany) was inserted using a nerve stimulator (Stimuplex S®; B. Braun Medical) with a starting output of 1.5 mA and 2 Hz. The needle was advanced until quadriceps twitches were elicited with a current between 0.3 and 0.5 mA. After negative aspiration for blood, the local anaesthetic solution was injected over ~3 min in 5 ml increments. The time at which all of the local anaesthetic solution had been injected was taken as time zero. Patients remained in this position and the i.v. solution was administered.

Sensory blockade of the femoral nerve was assessed 5 and 7.5 min after time zero. Sensory testing for thermoanaesthesia was performed on the mid-anterior thigh with ethyl chloride spray and compared with the contralateral side. Sensation was scored as 0=no difference, 1=less cold, 2=not cold. Sensory onset was defined as complete thermoanaesthesia (i.e. score=2). If no evidence of femoral sensory block was detectable at 7.5 min, the anaesthetist proceeded with spinal anaesthesia and subsequently the patient was assessed in the recovery ward for evidence of lumbar plexus blockade after resolution of spinal anaesthesia.

Either a 25 G Whitacre or a 22 G Yale needle was used to administer 17.5 mg bupivacaine 0.5% intrathecally. Rectal paracetamol 1 g and diclofenac 75 mg i.v. were then administered.

Intraoperative hypotension was defined as a decrease in systolic blood pressure from a baseline of $\geq 30\%$ and was treated with increments of ephedrine 6 mg i.v. Further midazolam 1–2 mg i.v. was titrated to a maximum total dose of 10 mg as clinically indicated. Maintenance and replacement fluids consisted of Hartmann's solution and were administered at the discretion of the attending anaesthetist.

After surgery the following data were recorded 8, 14, 20 and 24 h after performance of the PCB, by nursing staff unaware of the group allocations: time to first morphine analgesia, femoral nerve and lateral femoral cutaneous (LFC) nerve sensory block, obturator nerve motor block, pain scores at rest, presence of nausea/vomiting, sedation, heart rate, blood pressure and 24-h cumulative morphine consumption. Patients were cared for in a five-bed recovery ward for the first 24 h after surgery.

Sensory block of the femoral nerve (anterior thigh) and LFC nerve (lateral thigh) were evaluated using ethyl chloride spray and compared with the contralateral leg. Sensation was scored as described earlier. Blockade of the obturator nerve was evaluated by degree of motor block. Patients were asked to adduct their thigh and scored as 0=normal power, 1=weakness in adduction, 2=paralysis of adduction. Offset of sensory block in the femoral and LFC nerve distributions was defined as return to normal sensation. Offset of obturator motor block was defined as return to normal adductor power. For the purpose of data analysis, persistence of sensory or motor block at 24 h was recorded as offset at 24 h.

Pain was assessed using a standard verbal rating score for all patients, with 0=no pain and 10=worst pain imaginable. Pain was assessed at rest only to avoid prosthesis dislocation. Nausea and/or vomiting were recorded as present or absent. Antiemetic administration (intramuscular cyclizine 50 mg every 8 h if required) in the 24-h period was recorded. Sedation was scored as 0=awake, 1=drowsy, 2=asleep but rousable and 3=comatose. No sedatives were administered in the first 24 h after block insertion. Hypotension was defined as described earlier. Bradycardia was defined as a heart rate less than $60 \text{ beats min}^{-1}$.

Table 1 Patient characteristics. Data are mean (range) or mean (SD). No significant differences

Variable	Group L (n=21)	Group T (n=20)	Group IT (n=19)
Age (yr)	68 (50–83)	66 (49–79)	69 (54–83)
Gender (M/F)	10/11	11/9	7/12
Weight (kg)	77 (13)	77 (9)	79 (14)
ASA I/II/III	4/16/1	3/15/2	5/9/5
Arthroplasty (hip/knee)	12/9	15/5	13/6

Nursing staff administered paracetamol 1 g every 6 h and diclofenac 75 mg every 12 h irrespective of pain status. Patients were given morphine 0.15 mg kg⁻¹ i.m. when they requested supplementary analgesia and at 4-hourly intervals thereafter as required. Duration of analgesia was defined as the time from completion of block injection (time zero) to first administration of morphine. For the purpose of data analysis, patients who did not require morphine within 24 h had the time to first morphine analgesia recorded as 24 h. Twenty-four hours after surgery, cumulative morphine consumption was noted.

The study sample size was determined from previous work¹⁰ and our own data.¹¹ Based on $\alpha=0.05$, $\beta=0.2$ and seeking a difference of 3.5 h in the interval to first morphine administration (representing an increase of ~40% in PCB analgesic duration) with an estimated standard deviation of 4 h, a sample size of 19 per group was calculated.

Statistical analysis was performed with GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA USA; www.graphpad.com). Continuous parametric data were analysed using one-way ANOVA with Tukey's test for post-testing. Non-parametric data were analysed using the Kruskal–Wallis test with Dunn's test for post-testing. Proportional data were analysed using Fisher's exact test. Data are presented as mean (SD) or median (range). $P<0.05$ was taken as statistically significant.

Results

After randomization, 21 patients were allocated to group L, 20 patients to group T and 19 patients to group IT. The three groups were similar in terms of age, gender, weight, ASA classification, and surgery type (Table 1). Lumbar plexus block and spinal anaesthesia were successful in all patients.

The interval [h; mean (SD)] from time of completion of block injection to first morphine administration was similar in group L [11.2 (6.6)], group T [14.5 (8.0)] and group IT [14.6 (6.8)] ($P=0.35$). Twenty-four-hour cumulative morphine (mg) requirements [mean (SD)] were also similar between the three groups [group L, 21.9 (10.1); group T, 19.8 (6.7); group IT, 16.5 (9.5)]. These data are only for those patients who received morphine (group L, $n=18$; group T, $n=12$; group IT, $n=15$). The number of patients not receiving morphine within 24 h was seven in group T, four in group IT and three in group L ($P=0.28$). Onset of femoral nerve

Table 2 Duration (h) of sensory and motor block. Data are median (range). No significant differences

Variable	Group L	Group T	Group IT
Femoral nerve	24 (20–24)	24 (8–24)	24 (14–24)
LFC nerve	24 (20–24)	24 (14–24)	24 (14–24)
Obturator nerve	24 (14–24)	24 (8–24)	24 (14–24)

Table 3 Pain verbal rating scores. Data are median (range). T=time (h) after block. * $P<0.05$

Time interval	Group L	Group T	Group IT
T8	2 (0–8)	0.5 (0–9)	0 (0–8)
T14	2 (0–8)	0 (0–6)	0 (0–7)
T20	2 (0–8)*	0 (0–9)	0 (0–8)
T24	0 (0–7)	0 (0–4)	1 (0–9)*

Table 4 Ephedrine usage and number of patients with adverse effects (n). Data are mean (SD). ^a $n=14$; ^b $n=8$; ^c $n=10$ (n =number of patients who received ephedrine for treatment of hypotension)

Adverse effect	Group L (n=21)	Group T (n=20)	Group IT (n=19)
Intraoperative ephedrine (mg)	21 (11) ^a	23 (19) ^b	17 (8) ^c
Postoperative bradycardia	4	5	6
Postoperative hypotension	4	3	2
Nausea/vomiting	3	5	5
Antiemetic administered	3	4	4

sensory block occurred 7.5 min after block in 11 patients in group L, six patients in group T ($P=0.21$) and eight patients in group IT ($P=0.55$). The duration of femoral or LFC nerve sensory block or obturator nerve motor block was similar between groups (Table 2).

There were no differences in pain scores between groups at any of the four time points except at 20 h (group T vs group L, $P=0.048$) and 24 h (group T vs group IT, $P=0.047$) after block (Table 3).

Sedation scores [median (range)] were 0 (0–2) for all groups at each time point, except at 14 h, when patients in group IT [1 (0–2)] were more sedated than those in group L [0 (0–2)] ($P=0.02$).

Adverse effects, including episodes of intraoperative hypotension, indicated by ephedrine requirements were also similar in terms of nature and incidence in the three groups (Table 4).

Discussion

The results of this study indicate that the use of tramadol as a perineural or i.v. adjunct neither prolongs nor augments analgesia or anaesthesia in the setting of PCB with levobupivacaine 0.5%.

There are a number of possible mechanisms of action supporting the rationale for using tramadol as an adjunct

for regional anaesthesia. First, tramadol's monoaminergic actions include agonism at peripheral α_2 receptors, suggesting a role in nerve blocks similar to that of clonidine.¹³ Secondly, the presence of serotonin (5-hydroxytryptamine, 5-HT) subtype 3 (5-HT₃) receptors on peripheral nerve endings and in the dorsal laminae of the spinal cord indicates possible peripheral sites of analgesic action for tramadol. Tramadol increases 5-HT concentrations both by inhibiting reuptake and stimulating release. The role of 5-HT₃ receptors in analgesia is further supported by the findings that the 5-HT₃ antagonist ondansetron inhibits tramadol's analgesic effects.¹⁴ Finally, tramadol has local anaesthetic properties possibly by blocking K⁺ channels.¹⁵ The direct application of tramadol to rat sciatic nerves results in conduction block,⁶ and in humans intradermal administration of tramadol provides local anaesthesia for minor skin procedures.¹⁶

Direct comparison of studies involving tramadol for regional anaesthesia is difficult, as duration of nerve block has been defined in terms of duration of postoperative analgesia^{9,10} or of duration of anaesthesia.⁷ Furthermore, few studies have included a systemic tramadol group.^{7,17}

Studies of adjunctive tramadol in peripheral nerve blocks are few and have investigated tramadol's effects when combined with a local anaesthetic. Kapral and colleagues demonstrated that the addition of tramadol 100 mg to mepivacaine 1% for axillary plexus block prolonged sensory and motor block compared with mepivacaine alone or axillary block with tramadol 100 mg i.v.⁷ However, Robaux and colleagues failed to demonstrate an increase in sensory or motor block when tramadol was combined with mepivacaine 1.5% for brachial plexus block. Tramadol increased postoperative analgesia duration in a dose-dependent manner; however, a systemic tramadol group was not included in their study.⁸

Our finding that tramadol did not prolong analgesia or anaesthesia in the setting of PCB is further supported by the fact that no differences in block onset, 24-h morphine consumption or pain scores between the tramadol and control groups were found. Application of our findings in other clinical settings may not be appropriate. The local anaesthetic we used, levobupivacaine, is much longer-acting than mepivacaine and also has vasoconstrictor properties.¹⁸ The long duration of analgesia (11 h), as measured by time to first morphine administration, provided by levobupivacaine alone may have obscured a possible effect of tramadol. Tramadol added to ropivacaine 0.75% for brachial plexus block provided only ~9 h of analgesia.⁴ Secondly, the administration of tramadol into a compartment compared with placement in the brachial plexus sheath may affect drug concentrations. The concentration of tramadol 0.375% used in our study is less than the concentration of 0.5% that was the most effective dose in the study of Robaux and colleagues.⁸ Direct application of tramadol 1.25% in contrast to 2.5 and 5% to rat sciatic nerve failed to demonstrate a difference in amplitude reduction compared with saline.⁶

The physical dispersal of solution within the psoas compartment may affect local neural concentrations with consequent reductions in its direct neural effects.¹¹ Our use of tramadol 1.5 mg kg⁻¹ was based on dosages described in the literature at the commencement of our study.

We chose to study patients undergoing hip and knee arthroplasty as PCB provides excellent postoperative analgesia after both procedures with median visual analogue scores (VAS) of 10 mm at 24 h.^{12,19} While both joints receive innervation from the lumbar plexus and sciatic nerve,²⁰⁻²² studies show that blockade of the sciatic component is clinically unimportant for postoperative analgesia.^{12,22} However, the addition of obturator nerve blockade to femoral nerve block provides superior analgesia than femoral block alone.^{12,23} We believe that in the setting of peripheral nerve blockade the efficacy of postoperative analgesia is comparable for hip and knee arthroplasty.

The power of our study was based on an original estimate of a standard deviation of 4 h for time to first morphine analgesia. The standard deviation varied from 6.6 to 8 h; therefore it is possible that a type II error may have occurred. We had estimated the standard deviation from preliminary data investigating clonidine's effect on PCB and from work investigating tramadol combined with caudal bupivacaine.^{10,11} For the study to have a power of 80%, 63 patients would have been required per group.

The measurement of pain using VAS is common but has proved difficult to administer in the older orthopaedic population, with over half of patients unable to complete a VAS.²⁴ A verbal numerical scale was used as these have been shown to correlate with VAS in a number of patient settings,²⁵⁻²⁷ and we have used this scale successfully in a similar setting.¹¹

In conclusion, our data do not support a clinically important local anaesthetic or peripheral analgesic effect of tramadol as adjunct to psoas compartment block with levobupivacaine 0.5%.

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