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RESEARCH

A randomised trial to compare the effect of addition of clonidine or fentanyl to hyperbaric ropivacaine for spinal anaesthesia for knee arthroscopy

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Objectives: To evaluate the clinical effects of hyperbaric ropivacaine alone and with clonidine or fentanyl for spinal anaesthesia for knee arthroscopy.
Methods: Sixty ASA I/II patients were randomised to receive spinal anaesthesia with hyperbaric ropivacaine alone (Group R), or with clonidine 15 µg (Group RC) or fentanyl 30 µg (Group RF). The sensory and motor block, time to micturition and side effects were assessed.
Results: The three groups were similar in mean time to onset of sensory block at T10, height of block and time to maximum block. Sensory regression to S2 took longer in Groups RF and RC compared with Group R ($p = 0.001$ and $p < 0.01$, respectively). Time to requirement of rescue analgesia was longer in Groups RF and RC compared with Group R ($p = 0.023$ and 0.002, respectively). Time for complete regression of motor block and time to voiding were longer in group RC compared with group R ($p = 0.022$ and $p = 0.013$, respectively).
Conclusion: The addition of fentanyl 30 µg to hyperbaric ropivacaine may be superior to the addition of clonidine 15 µg for knee arthroscopy as it provides a similar prolongation of sensory block and analgesia without prolonging motor block and time to micturition.

Keywords: ambulatory; clonidine; fentanyl; ropivacaine; spinal anaesthesia

Introduction

Arthroscopic procedures for the knee have been done almost exclusively as ambulatory procedures for the past several years in most countries. An appropriate anaesthetic technique is required for an uncomplicated recovery with minimal pain. Spinal anaesthesia is usually adequate for these procedures but patient discharge, even after an uncomplicated spinal anaesthetic, may be delayed by surgical pain, nausea and vomiting, or unresolved neuraxial block. There are also data to suggest that general anaesthesia may in fact be better and may be associated with faster recovery and fewer side effects.[1] The evidence for transient neurological symptoms (TNS) associated with the short-acting spinal anaesthetic lidocaine has led to the use of alternative drugs such as bupivacaine, levobupivacaine or ropivacaine. Ropivacaine is the pure S enantiomer of propivacaine and is a long-acting amide local anaesthetic which is associated with a lower grade of motor block, a shorter duration of action than bupivacaine and a reduced potential for CNS and cardiac toxicity, making it a possible alternative to lidocaine for shorter outpatient procedures.[2]

The dose of local anaesthetic can be reduced by the addition of adjuvants like opioids and α2-adrenergic agonists. Subarachnoid fentanyl is known to provide rapid onset of analgesia, improve surgical blockade quality and enhance the effect of small doses of subarachnoid bupivacaine.[3]

Clonidine, on the other hand, while also potentiating spinal anaesthesia, does not induce pruritus or respiratory depression, which are common side effects when opioids are used. When 1–2 µg/kg of clonidine is combined with local anaesthetics intrathecally, a significant improvement in the intensity of block and duration of sensory and motor block has been reported.[4,5] However, at these doses, bradycardia, hypotension and sedation may be seen.[6]

As ropivacaine is a drug in which there is a differential nerve blockade with motor function recovering earlier than sensory function, we wished to study the effect of co-administering either fentanyl 30 µg or clonidine 15 µg with 15 mg ropivacaine intrathecally in order to enhance the intensity and prolong the duration of analgesia provided by ropivacaine without deducting from the purported advantages of ropivacaine and allowing an earlier discharge to home readiness.

Material and methods

After approval by the Institutional Ethics Committee, this prospective, randomised, double-blind study was conducted on 60 patients aged 18–60 years of ASA class I/II, undergoing knee arthroscopy. The study was registered at the Clinical Trials Registry (http://www.ctri.in), registration number CTRI/2010/091/00549. Written informed consent was obtained from all patients. Exclusion criteria included obesity (BMI > 30 kg/m^2), allergy to study drugs, inability to comply with the study procedure, i.e. psychiatric disorder, language problems, history of chronic pain, alcohol, drug or medication abuse, pregnancy and those patients with other absolute contraindications to spinal anaesthesia.

To achieve the same quality of anaesthesia as 8 mg bupivacaine, it has been found that 12 mg ropivacaine must be administered.[7] Kallio et al.[8] concluded that the duration of sensory block of ropivacaine was two-thirds and the duration of motor block was half when compared with bupivacaine, with calculations based on the duration-per-milligram of the local anaesthetic. A dosage of 15 mg ropivacaine for spinal anaesthesia was used in all

patients, as the general intrathecal dose of bupivacaine being used for arthroscopic knee procedures is 10 mg since the duration of many reconstructive arthroscopic procedures is about 2–3 hours. An additional 30 µg intrathecal fentanyl was added in the second group and 15 µg intrathecal clonidine in the third group. The three groups were compared with regard to motor and sensory blockade, haemodynamic effects and the duration of analgesia and time to void.

The 60 patients were randomly allocated to one of the three study groups according to a computer-generated randomisation table to receive spinal anaesthesia with 15 mg hyperbaric ropivacaine (Group R; 2 ml of 0.75% ropivacaine + 0.4 ml of 50% dextrose + 0.6 ml normal saline), 15 mg hyperbaric ropivacaine with 15 µg clonidine (Group RC; 2 ml of 0.75% ropivacaine + 0.4 ml 50% dextrose + 0.1 ml preservative free clonidine + 0.5 mL normal saline) or 15 mg hyperbaric ropivacaine with 30 µg fentanyl (Group RF; 2 ml of 0.75% ropivacaine + 0.4 ml of 50% dextrose + 0.6 ml fentanyl). The group allocations of the patients were delivered in an opaque sealed envelope just before surgery.

All the patients received midazolam 7.5 mg orally 1 hour before being moved to the operating room (OR), where standard intraoperative monitoring, comprising electrocardiography, pulse oximetry and noninvasive blood pressure (NIBP), was instituted. A suitable peripheral vein was cannulated with an 18-G cannula and preloading was commenced with 500 ml of Ringer lactate solution. Baseline values of heart rate and blood pressure were noted and the patient was then placed in the lateral position with the side to be operated dependent and horizontal position of the spine was verified using a spirit level. All study solutions were prepared aseptically in identical syringes by an anaesthetist not involved with subsequent administration and patient assessment. The investigator was blinded as to the identity of the solution. All solutions were administered at room temperature. Under aseptic conditions, after local skin infiltration with 1% lidocaine, spinal puncture was performed in the midline in the L3-L4 interspace using a 25-G spinal needle with the bevel directed towards the dependent (operative) side of the patient. The study drug was administered slowly over approximately 1 minute and the patient remained in the lateral decubitus position for 10 minutes after completion of injection of spinal drug. This was considered time zero (T0).

After turning the patient supine, a tourniquet was applied on the operative thigh and inflated to a pressure 100 mmHg above the patient's baseline systolic pressure. Oxygen was administered by face mask if required (SpO_2 < 95%). Heart rate and blood pressure were recorded before intrathecal injection and thereafter at 2 and 5 minutes and then every 5 minutes during the surgery. A decrease in systolic blood pressure of more than 30% from the baseline was treated with 5 mg of intravenous ephedrine. A heart rate less than 50 beats/minute was treated with 0.6 mg intravenous atropine.

The degree of motor block was assessed by the modified Bromage scale[9] (Grade 0 is no motor block; Grade 1 is inability to raise extended leg but able to move knees and feet; Grade 2 is inability to raise extended leg and move knee but able to move feet; Grade 3 is complete block of lower limb). Assessment was done at 10 minutes after injection and then every 5 minutes until maximum block was achieved or until surgery was commenced.

Sensory block height was assessed by loss of sensation to pin prick on the dependent side using a 22-G blunt hypodermic needle in the mid-clavicular line at 2 and 5 minutes and then at 5 minute intervals after injection until 2 consecutive levels of sensory block were identical. Surgery was initiated once the level of sensory block reached T12. Block was considered adequate when the sensory level reached T10.

Midazolam 1 mg was administered intravenously for sedation if required. If the sensory block was not adequate for the planned surgery at 30 minutes, general anaesthesia was administered and it was considered a failed block. Successful unilateral spinal anaesthesia was defined as surgical anaesthesia (loss of pinprick sensation at T10, and motor score 2 or 3) on the dependent side only, while the nondependent side maintained both somatic sensibility to pinprick test and motor score < 1 which was assessed at 10 and 30 minutes after spinal injection.

After the completion of surgery, Surgeon Satisfaction Score and Quality of Anaesthesia (assessed by senior anaesthetist/senior resident) was noted as excellent, satisfactory or unsatisfactory.

The quality of intraoperative analgesia was assessed by the patient on a four-point scale: (1) Perfect analgesia, no sensation at all from surgical site; (2) Adequate analgesia, sensation of motion only; (3) Inadequate analgesia, discomfort but patient declines additional analgesia; (4) Major discomfort, additional analgesia required (in such a case the patient was required to receive intravenous boluses of 25 µg fentanyl as required).

After surgery, the patients were transferred to the post-anaesthesia care unit (PACU) where monitoring continued. At arrival in the PACU and then at 15-minute intervals, motor block, sensory block, heart rate and NIBP were assessed till discharge criteria (no difficulty in breathing, stable blood pressure and heart rate, fully oriented, ability to walk and dress, ability to drink without nausea and vomiting, ability to void and no/slight pain) were met. Assessment of motor block was then done at 15-minute intervals after completion of surgery until normal motor function returned. Assessments of sensory block were continued every 15 minutes after completion of surgery until regression to the S2 dermatome. Time to regression of sensory block to S2 was noted. Regression of sensory block to S2 indicated discharge to home readiness.

Duration of analgesia was taken as time to the demand of first analgesic at which time diclofenac sodium 1 mg/kg was administered intravenously. Time from intrathecal injection to spontaneous micturition was also noted. If any patient had difficulty in micturition (i.e. patient discomfort despite hot water bottle administration or allowing the patient to sit on the edge of the bed), then bladder catheterisation was performed. Any adverse effects in the postoperative period like nausea, vomiting, sedation, respiratory depression, dryness of mouth, skin rash, itching, headache, backache or neurological symptoms were noted as plus or minus. The patients were interviewed telephonically 2–3 days after discharge about headache, backache, pain radiating to the back and/or sensory disturbances in areas not related to the surgical procedure etc.

The calculation of the required sample size was based on mean and standard deviation of complete regression of spinal block after unilateral spinal anaesthesia for outpatient knee arthroscopy reported in a previous investigation by Casati et al.[10] Twenty patients per group were required to detect a 30-minute difference in time for complete regression of spinal anaesthesia with an expected effect size to standard deviation ratio of 0.9, and accepting a two-tailed α error of 5% and a β error of 20%.

Statistical analysis was performed using commercially available software SPSS 17.0 (SPSS Inc., Chicago, IL). The time taken to achieve maximum motor block, T10 level sensory block, maximum sensory block and time to complete motor regression and sensory regression to sacral dermatome S2 were assessed by one-way ANOVA test. Fisher's exact t-test was used for multiple comparisons of different data between the groups. Correction for multiple comparisons was done by Bonferris correction. Data were expressed as mean ± standard deviation. A p-value of < 0.05 was considered statistically significant. Continuous variables were presented as mean ± SD or as median (range); categorical data were presented as number (%).

Results

The 60 patients included in the study were comparable with respect to age, sex, ASA physical status, weight where height (p > 0.05) (Table 1). Readiness for surgery was achieved in all patients in all three groups and the spinal block success rate was 100%. No differences in the onset time of surgical block were observed among the three groups. There were no statistically significant differences in onset of sensory block to the T10 dermatome and time to achieve maximum sensory block between the three groups. The maximum height of sensory block achieved on the dependent side was T4 in Group R (in seven patients) and Group RC (in six patients) and T2 in Group RF (in two patients). The median height of sensory block was T5 in Group R and T6 in Group RF and RC.

The duration of sensory block at T10 was similar in all groups. However, times for sensory regression of the block to S2 dermatome were significantly higher in Group RF (262.6 ± 44.67 min) compared with Group R (210.65 ± 39.39 min) (p = 0.001) and in Group RC (262.5 ± 37.7 min) as compared with Group R (210.65 ± 39.39 min) (p < 0.01). The duration of sensory blockade in Groups RF and RC was similar (p = 1) (Table 2).

The median time from end of intrathecal injection to achieving maximum motor blockade was 10 minutes for all 3 groups, i.e. when first tested after making the patient supine, all the patients had attained maximum level of motor block. All patients in the three groups achieved a modified Bromage score of 3 by this time except one patient in Group R who attained a Bromage Score of 1.

The time taken for complete regression of motor block was significantly different between the three groups (p = 0.005). It was significantly longer in Group RC (156.0 ± 42.4 min) compared with Group R (123.9 ± 26.59 min) (p = 0.022) and equivocal between Groups RF (128.2 ± 24.9 min) and RC (156.0 ± 42.4 min) (p = 0.050) (Table 3). No patient in any group attained exclusively unilateral anaesthesia as per definition.

The time to requirement of rescue analgesia was longer in Groups RF (382.5 ± 122.35 min) and Group RC (390.5 ± 82.5 min) compared with Group R (284.6 ± 95.35 min) and these differences were statistically significant (p = 0.023 and 0.002, respectively) (Table 4). The quality of intraoperative analgesia reported by the patients on a four-point scale was graded as perfect in all the groups. Surgeon satisfaction score and quality of anaesthesia (as assessed by a senior anaesthetist not participating in the study) was noted as excellent in all patients. Time to micturition was significantly prolonged in Group RC (419.5 ± 83.8 min) as compared with Group R (333.15 ± 96.05 min) (p = 0.013). There was no prolongation of time to voiding in Group RF compared with Group R (Table 4).

No patient in any group had significant hypotension requiring ephedrine. Two patients in Group R had bradycardia requiring atropine and the height of sensory block in these patients was T4. There was no significant difference in heart rate and noninvasive blood pressure between the three groups intraoperatively. In Group RC patients there was a significantly lower heart rate recorded up to five hours after spinal administration of the study solution and a significantly lower diastolic blood pressure

Table 1: Patient characteristics: values are presented as Mean ± SD or as number

	Group R (n = 20)	Group RF (n = 20)	Group RC (n = 20)	p-value
Age (years)	32.3 ± 13.3	37.4 ± 8.98	31.8 ± 11.1	NS
Sex (M/F)	18/2	17/3	18/2	NS
ASA physical status (I/II)	19/1	18/2	19/1	NS
Weight (kg)	60.7 ± 7.2	61.65 ± 7.74	62.7 ± 9.92	NS
Height (cm)	164.45 ± 4.87	164.05 ± 5.88	164.5 ± 6.31	NS

Table 2: Characteristics of sensory blockade: values are presented as Mean ± SD or as median

	Group R (n = 20)	Group RF (n = 20)	Group RC (n = 20)	p-value
Onset to T10 (min)	2.7 ± 1.9	3.1 ± 2.26	2.3 ± 0.94	0.429
Time to maximum sensory block (min)	11.3 ± 5.17	11.7 ± 6.15	10.4 ± 5.86	0.765
Median height of sensory block attained	T_5	T_6	T_6	
Duration at T10 (min)	131.9 ± 37	167.3 ± 40.7	157.8 ± 59.06	0.0537
Time for complete regression of sensory block (min)	210.65 ± 39.39	262.6 ± 44.67	262.5 ± 37.7	0.000* R vs. RF 0.001* R vs. RC < 0.01* RF vs. RC 1.00

Note: *p-value < 0.05.
There was a statistically significant difference in the three groups in the time taken for regression of the sensory block (p = 0.000). Time taken for complete regression of sensory block was significantly longer in Group RF as compared to Group R (p = 0.001) and in Group RC as compared to Group R (p<0.01).

Table 3: Characteristics of motor blockade: values are presented as Mean ± SD or as median

	Group R (*n* = 20)	Group RF (*n* = 20)	Group RC (*n* = 20)	*p*-value
Median time to reach maximum motor block (min)	Within 10 min	Within 10 min	Within 10 min	
Number of patients in whom Grade 3 motor block achieved	19	20	20	0.5
Max. modified Bromage score achieved	3	3	3	
Time taken for complete motor regression (min)	123.9 ± 26.59	128.2 ± 24.9	156.0 ± 42.4	0.005* R vs. RF 0.934 R vs. RC 0.022* RF vs. RC 0.05*

Note: **p*-value < 0.05.
There was a statistically significant difference in time taken for regression of motor block in the three groups ($p = 0.005$). Motor blockade was significantly longer in Group RC as compared to Group R ($p = 0.022$) and equivocal between Groups RF and RC ($p = 0.05$)

Table 4: Duration of analgesia and time to micturition: values are presented as Mean ± SD

	Group R (*n* = 20)	Group RF (*n* = 20)	Group RC (*n* = 20)	*p*-value
Time to requirement of first analgesic (min)	284.6 ± 95.35	382.5 ± 122.35	390.5 ± 82.5	0.002* R vs. RF 0.023* R vs. RC 0.002* RF vs. RC 0.993
Time to void (min)	333.15 ± 96.05	393.5 ± 128.28	419.5 ± 83.8	0.034* R vs. RF 0.273 R vs. RC 0.013* RF vs. RC 0.837

Note: **p*-value < 0.05.
There was a statistically significant difference in time to requirement of first analgesic among the three groups ($p = 0.002$). Time to requirement of first analgesic was significantly longer in Group RF as compared to Group R ($p = 0.023$) and in Group RC as compared to Group R ($p = 0,002$).
The time taken to void urine was also significantly different in the three groups ($p = 0.034$) and was significantly longer in Group RC as compared to Group R ($p = 0.013$).

recorded at about six hours. One patient in Group RF had pruritus. No patient in any group had any other complication.

Discussion

Rapid recovery from motor and sensory block is required to facilitate early mobilisation after day care surgeries such as knee arthroscopy. Many drugs and their combinations have been tried to achieve this. The use of hyperbaric lidocaine 5% has declined due to concerns of cauda equina syndrome and transient neurological symptoms, which has aroused interest in alternative local anaesthetics and combinations to produce spinal anaesthesia of reliably short duration.

Kallio and colleagues[8] found that ropivacaine 15 mg provided a faster recovery of motor block, but a similar duration of sensory block to bupivacaine 10 mg. Wahedi et al.[11] reported that loss of sensation at the T10 dermatome was achieved with 15 mg of ropivacaine, which prompted the use of this dose. The ED_{50} and ED_{95} for spinal ropivacaine in lower limb surgery of 50 minutes' duration or less have been found to be 7.6 and 11.4 mg, respectively. This provides a useful guide for clinicians to choose the optimal dose of spinal ropivacaine under different clinical situations.[11] Fettes et al.[12] provided further evidence that a dose of 15 mg hyperbaric ropivacaine produces predictable and reliable spinal anaesthesia for a variety of surgical procedures of a relatively short duration. In the study 0.4 ml of 50% dextrose was added to 2 ml of 0.75% ropivacaine to make the solution hyperbaric and improve the success rate. The concentration of glucose used (66.6 mg/ml) was the easiest concentration to dispense using readily available solutions, and provided a solution that was sufficiently hyperbaric for its purpose.

Cappelleri et al.[13] found a strictly unilateral sensory block in 73% of patients receiving ropivacaine 7.5 mg 30 minutes after injection and unilateral motor block was observed in 94%. None of the patients in the study attained entirely unilateral anaesthesia probably because both the dose and volume were too high.

The addition of both fentanyl 30 µg and clonidine 15 µg prolonged the duration of sensory block. This prolongation of sensory block by addition of adjuvants like fentanyl and clonidine has been proven by several earlier investigators.[5,7,14–17] The antinociceptive properties of clonidine indicate that it might be useful as an alternative to intrathecal opioids for postoperative analgesia. However, while there was no significant prolongation of motor block in patients given intrathecal fentanyl, there was a significant prolongation of the motor block in patients who received intrathecal clonidine 15 µg along with ropivacaine. Van Tuijl et al.[15] found that the addition

of 15 µg clonidine to 5 mg hyperbaric bupivacaine prolonged the duration of motor block by 25 minutes and seemed to improve the block quality in outpatient knee arthroscopy. The addition of 30 µg of clonidine instead of 15 µg did not further improve the quality of the block. M De Kock et al.,[16] on the other hand, found that while 15 µg intrathecal clonidine was found to significantly improve the quality of the anaesthesia provided by 8 mg intrathecal ropivacaine in patients undergoing ambulatory knee arthroscopy, this was obtained without compromising the benefits of low-dose intrathecal ropivacaine, such as short-lasting motor block, early mobilisation and micturition.

Urinary retention has been attributed to intrathecal opioids. However, voiding, in this study, was delayed more in the RC group compared with the RF group. Van Tuijl et al.[15] reported a delay in spontaneous voiding with 15 µg of clonidine. This has been reported by other authors too and may be attributed to slightly lower intraoperative blood pressures due to the haemodynamic effects of clonidine resulting in less urine production.

Clonidine, after neuraxial or systemic administration, affects arterial BP in a complex manner because of opposing actions at various sites. Whilst the α2-adrenergic agonists produce sympatholysis and reduce arterial BP through effects on specific brainstem nuclei and on sympathetic preganglionic neurons in the spinal cord, these effects are counteracted by direct vasoconstriction resulting from the α2-adrenergic agonists on the peripheral vasculature. As a result, the dose response for neuraxial clonidine on arterial blood pressure in humans is generally considered to be U-shaped. Combining α2-adrenergic agonists with local anaesthetics can potentially increase the degree of sympatholysis and the resulting hypotension.[17–19] In the present study, there was a significantly lower heart rate recorded up to five hours after spinal administration of the study solution and a significantly lower diastolic blood pressure recorded at about six hours in those patients who received clonidine with ropivacaine. However, no episodes of hypotension or bradycardia were noted in any patient.

Addition of both fentanyl 30 µg and clonidine 15 µg significantly prolonged the duration of sensory blockade when given with 15 mg ropivacaine made hyperbaric by the addition of glucose 6.66% and hence also prolonged the time to requirement of first rescue analgesic. The prolongation of the time for complete regression of the motor block by clonidine may be desirable when it is combined with a local anaesthetic with lesser motor blockade like ropivacaine for longer procedures but may be undesirable when early patient mobilisation is required. The prolongation of the time to micturition by clonidine 15 µg may also not be desirable for ambulatory surgery patients.

The addition of fentanyl 30 µg may be superior to addition of clonidine 15 µg for ambulatory knee arthroscopy as it provides similar prolongation of sensory block without prolonging the duration of motor block and delaying time to voiding of urine. No patient in any group had excessive sedation, respiratory depression, shivering, nausea and vomiting or residual neurological deficit, post-dural puncture headache or transient neurological symptoms at follow-up.

However, one of the drawbacks of the present study was that the baricity of the final spinal injectates amongst the three groups was not measured. This may have also influenced the results (knowing that the volume of injectate was equal amongst the groups).

To conclude, an advantage of intrathecal ropivacaine is to induce less motor blockade than bupivacaine and its sensory blockade can be modified by the addition of fentanyl or clonidine. Addition of fentanyl, however, appears more suitable for day care surgery in terms of earlier return of mobility with similar duration of analgesia and earlier voiding compared with the addition of clonidine.

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