Original Article

# Low dose intrathecal clonidine and fentanyl added to hyperbaric bupivacaine prolongs analgesia in gynecological surgery

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## Abstract

**Background:** We undertook this study to ascertain if a small dose of clonidine (30 μg) when added to a bupivacaine-fentanyl mixture improves spinal analgesia, without producing side effects, as compared to a bupivacaine-fentanyl or a bupivacaine-clonidine mixture.

**Materials and Methods:** In this prospective, randomized, double-blind study, 75 (American Society of Anesthesiologists) ASA grade I-II patients, aged between 45 and 65 years, who were scheduled for vaginal hysterectomy with pelvic floor repair or non-descent vaginal hysterectomy under spinal anesthesia were recruited. The patients received hyperbaric bupivacaine (2.3 ml) with fentanyl 15 μg (Group BF) or clonidine 30 μg (Group BC) or both fentanyl (15 μg) and clonidine (30 μg) (Group BCF). The total amount of intrathecal mixture was constant (2.8 ml) in all the groups. Duration of sensory, motor block and effective analgesia, hemodynamic profile, postoperative pain score and analgesic requirements were recorded.

**Results:** The duration of effective analgesia, mean time till two-segment regression, and duration of sensory and motor block were significantly longer in group BCF as compared to group BC ($P \sim 0.002$), and in group BC as compared to group BF ($P \sim 0.01$). The incidence of intraoperative pain and requirement of postoperative analgesics in the first 24 hours was significantly more in group BF as compared to the other groups ($P \sim 0.01$). There was no difference in the hemodynamic profile between the groups.

**Conclusion:** Low-dose clonidine (30 μg) when added to a bupivacaine-fentanyl mixture increased the duration of effective analgesia and the duration of sensory and motor block in gynecological surgery. The incidence of intraoperative pain and requirement of postoperative analgesics was significantly less when clonidine was added to intrathecal bupivacaine with or without fentanyl.

**Key words:** Anesthetic, analgesia, bupivacaine, clonidine, fentanyl, postoperative, spinal

## Introduction

Clonidine has been used as an adjuvant in regional anesthesia in various settings, including spinal anesthesia. Co-administration of clonidine and bupivacaine produces enhanced analgesia than a mixture of bupivacaine and fentanyl.[1] Most of the studies have used clonidine in the dose range of 75 μg and above.[2-4] Dobrydnjov *et al.* reported a higher spread of analgesia during inguinal herniorraphy, in patients who received 30 μg clonidine with bupivacaine, as compared to those who received 15 μg clonidine with bupivacaine or bupivacaine alone.[5]

Clonidine has been used as a sole agent as well as admixed with opioids and local anesthetics in labor analgesia and gynecological surgeries.[2,6,7] Gautier *et al.* found that patients receiving 30 μg intrathecal clonidine with 2.5 or 5 μg sufentanil had a significantly longer lasting analgesia than those receiving 5 μg of sufentanil alone, during labor.[8]

In this study, we have used a lower dose of intrathecal clonidine (30 micro gm) to ascertain it's efficacy, when used with or without fentanyl.The aim of this study was to investigate whether the addition of low-dose clonidine to intrathecal bupivacaine and fentanyl increased the duration of effective analgesia, as compared to a mixture of bupivacaine-fentanyl or bupivacaine-clonidine in gynecological surgery.

## Materials and Methods

After obtaining the Institutional Research and Ethics Committee approval, written informed consent for this

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randomized, double-blind trial was obtained from 75 healthy female patients, scheduled to undergo vaginal hysterectomy with pelvic floor repair or non-descent vaginal hysterectomy (NDVH) under subarachnoid block. ASA grade I-II patients, with height ranging between 150 cm and 160 cm, were included in the study.

The patients were premedicated with oral alprazolam 0.25 mg at night and two hours prior to the surgery. In the Operating Room, the baseline parameters (pulse, blood pressure, $SpO_2$, and EKG) were recorded and intravenous infusion was started withRinger's Lactate solution administered at the rate of 10 ml/kg prior to the subarachnoid block. The patients were randomized to one of the following three groups:

Group I (BF)-0.5% Hyperbaric bupivacaine (2.3 ml) and fentanyl (15 μg) with saline 0.2 ml
Group II (BC)-0.5% Hyperbaric bupivacaine (2.3 ml) and clonidine (30 μg) with saline 0.3 ml
Group III (BCF)-0.5% Hyperbaric bupivacaine (2.3 ml) with fentanyl (15 μg) and clonidine (30 μg)

The total amount of the intrathecal mixture was constant (2.8 ml) in all the groups.

Under all aseptic precautions, a subarachnoid block was performed in the L3-L4 or L4-L5 interspace using a 25G Quincke spinal needle in the lateral position. The patients were randomly assigned to one of the three groups by the second author, using computer-generated random numbers, which were contained in a sealed envelope. This was handed over to another anesthesiologist drawing up the study drug in an unlabeled, sterile syringe. The intrathecal procedure, including administration of the drug, was done by the first author who remained blinded to its contents. Patient assessment and observations were also recorded by this blinded researcher in the Operation Theater as well as in the Recovery Room. The measured variables included the pulse rate, systolic and diastolic blood pressure, mean arterial pressure (MAP), onset, level, duration, and regression of the sensory and motor block, quality of analgesia, and sedation. The measurements were recorded every two minutes for the initial 10 minutes, every five minutes for the next 20 minutes, and subsequently every 15 minutes till the end of surgery. The level of the sensory blockade was assessed using a 25G short bevel needle and recorded as loss of sensation to pin prick. The onset of the sensory block and time taken for two-segment regression of the block and regression to L1 were noted. The onset of the sensory block was taken from the time of the intrathecal injection till the time the highest level of the block was achieved. Duration of the sensory block was taken from the time of maximum sensory block till regression of the block to L1. The sensory spread was calculated as the number of dermatomal segments blocked from S5.

The quality of intraoperative analgesia was evaluated by the patient at 30-minute intervals using the following four-point scale (1 — excellent analgesia, no sensation at all from the surgical site; 2 — adequate analgesia, sensation of motion only; 3 — inadequate analgesia, discomfort, but the patient declines additional analgesia; 4 — major discomfort, additional analgesics are necessary).[9] When the patient complained of major discomfort, which mainly occurred at the time of pulling of the uterus, repeated boluses of 25 μg IV fentanyl (≤100 μg) were administered by the anesthesiologist monitoring the patient. General anesthesia was administered when the intraoperative pain score exceeded score 4 (major discomfort, additional analgesics are necessary) and the patients remained uncomfortable despite being given 100 μg fentanyl. The motor block was determined according to the modified Bromage scale[3] (ranging from 0 = no motor block to 3 = complete motor block of both lower limbs). Duration of the motor blockade was taken from the time of intrathecal injection till no motor weakness could be detected.

All the patients were administered oxygen via a Ventimask. Ringer's Lactate was given in calculated doses according to the weight of the patient and period of fasting and adjusted as per blood loss during surgery. A fall of MAP by 30% of the baseline was treated with rapid infusion of 200 ml of Ringer's Lactate and 3 mg aliquots of injection mephentermine intravenously, in case there was no response to fluid administration. Bradycardia (<50/minute) was treated with intravenous atropine sulfate. The presence of side effects like nausea, vomiting, pruritus, and shivering were noted. Sedation was recorded using a graded score (ranging from 0 = awake to 5 = eyes closed, but unarousable to mild physical stimulation).[10]

Severity of pain was assessed at 30 minutes, one hour, two hours, four hours, 12 hours, and 24 hours postoperatively, using a 10 cm visual analog scale (VAS). The patients were given a rescue analgesic in the form of intramuscular diclofenac sodium (75 mg) when the VAS exceeded four; and the time of administration of the first as well as subsequent injections in 24 hours was noted. Duration of effective analgesia was taken from the time of intrathecal injection till the administration of the first rescue analgesic. The presence of any other side effect in the postoperative period was noted.

Statistical analysis was performed using the duration of effective analgesia as the primary outcome, with the Megastat software. Taking alpha 0.05 and sample size of 25 in each group, Power of the study was 70%. The Kruskal Wallis test

was used to compare categorical data and Analysis of Variance (ANOVA) was used for variable data. A $P$-value of $<0.05$ was considered to be statistically significant.

## Results

A total of 75 patients were studied, out of which two patients from the BF group were excluded as they required general anesthesia after 2 hrs of giving the block. The demographic profile was similar between the groups [Table 1].

Comparison of serial measurements of blood pressure and heart rate during surgery did not reveal any significant differences among the groups. Variations in the hemodynamic parameters (Heart rate, MAP) are shown in Figures 1 and 2.

The sensory level obtained was higher and onset of sensory block was faster in groups BC and BCF as compared to group BF and this was found to be statistically significant ($P \sim 0.003$) [Table2].

The mean time till two-segment regression, duration of sensory and motor block, and duration of effective analgesia were significantly longer in group BCF, as compared to groups BC and BF ($P$ value $\sim 0.002$) and in group BC ($P \sim 0.01$) as compared to group BF. All the patients, however, required a rescue analgesic in the postoperative period. The incidence of intraoperative pain and requirement of postoperative analgesics in the first 24 hours was significantly higher in group BF as compared to the other groups ($P \sim 0.01$) [Tables 2 and 3].

The incidence of intraoperative nausea and vomiting was comparable in all the groups. Shivering was significantly more in Group BF, as compared to the other groups (BF > BCF > BC) ($P \sim 0.001$). Sedation was significantly more in Group BC as compared to Groups BF and BCF ($P \sim 0.002$), as well as in Group BCFcompared to Group BF (BC > BCF > BF) ($P \sim 0.001$). However, sedation never exceeded grade 2 (drowsy). Requirement of mephentermine and additional fluids was similar in the three groups [Table 3].

## Discussion

Our study indicates that addition of 30 μg of clonidine to a mixture of 0.5% hyperbaric bupivacaine and 15 μg of fentanyl significantly prolongs the duration of effective analgesia and duration of the sensory and motor block, as compared to the bupivacaine — clonidine and bupivacaine — fentanyl combinations, without causing any significant side effects.

Clonidine is an alpha 2 agonist, which potentiates both sensory and motor blockade of local anesthetics.[11] The analgesic effect following intrathecal administration is mediated via the activation of postsynaptic alpha 2 receptors in the substantia gelatinosa of the spinal cord. It works by blocking conduction of the Aδ and C fibers, and also intensifies the conduction block of local anesthetics.[11]

**Table 1: Patient characteristics and surgical conditions**

| Demographic variables | Group BF $n = 25$ | Group BC $n = 25$ | Group BCF $n = 25$ |
|---|---|---|---|
| Height (cm) | 153±4 | 154±4 | 157±5 |
| Weight (kg) | 50±4.4 | 53.5±8.8 | 59.6±7.6 |
| Age (years) | 46.2±8.6 | 51.6±8.2 | 43.5±7.4 |
| Duration of surgery (minutes) | 127.8±25.7 | 112.8±26.4 | 108±35.7 |

*Group BF = Intrathecal bupivacaine-fentanyl, Group BC = Intrathecal bupivacaine-clonidine, Group BCF = Intrathecal bupivacaine-clonidine plus fentanyl, Values are mean ± SD*

**Table 2: Analgesic data**

| Variables | Group BF ($n = 25$) | Group BC ($n = 25$) | Group BCF ($n = 25$) |
|---|---|---|---|
| Dermatomal spread after intrathecal injection (dermatomes blocked) | 15±2 | 16±2* | 17±2† |
| Onset of sensory block (minutes) | 17.2±5.4 | 10.48±4.2* | 12.88±4.1† |
| Intraoperative pain (% of patients) | 40 ($n$=10) | 12* ($n$=3) | 0† |
| Regression to two segments (minutes) | 75±30 | 95±56* | 111±30†‡ |
| Duration of sensory block (minutes) | 142.2±14.7 | 177.8±-43.8* | 221±33.3†‡ |
| Duration of effective analgesia (minutes) | 176±40.8 | 323±99.5* | 426±152†‡ |
| Number of diclofenac injections in 24 hours | 2.66 (2-3) | 1.16 ( 1-2 )* | 1.06 (1-2)† |

*Group BF = Intrathecal bupivacaine-fentanyl, Group BC = Intrathecal bupivacaine-clonidine, Group BCF = Intrathecal bupivacaine-clonidine plus fentanyl, Values are mean ± S.D, *P < 0.05 for group BC versus group BF, †P < 0.05 for group BCF versus group BF, ‡P < 0.05 for group BCF versus group BC*

**Table 3: Intraoperative parameters**

| Intraoperative variables | Group BF ($n = 25$) | Group BC ($n = 25$) | Group BCF ($n = 25$) |
|---|---|---|---|
| Duration of motor block (minutes, mean ± SD) | 166.2±15.8 | 206.6±43.6* | 254±33.8†‡ |
| Nausea and vomiting (% of patients) | 16 ($n$=4) | 12 ($n$=3) | 8 ($n$=2) |
| Shivering (% of patients) | 96 ($n$=24) | 8* (n=2) | 20† ($n$=5) |
| Sedation (% of patients) | 12($n$=3) | 88* ($n$=22) | 44†‡ ($n$=11) |
| Mephentermine (Total dose, mg, mean ± SD) | 2.7±1.7 | 3.5±2.2 | 3.7±3.2 |
| Additional Lactated Ringer's Solution (ml, mean ± SD) | 1011±686 | 1026±659 | 1001±603 |

*Group BF = Intrathecal bupivacaine-fentanyl, Group BC = Intrathecal bupivacaine-clonidine, Group BCF = Intrathecal bupivacaine-clonidine plus fentanyl, *P < 0.05 for group BC versus group BF, †P < 0.05 for group BCF versus group BF, ‡P < 0.05 for group BCF versus group BC*

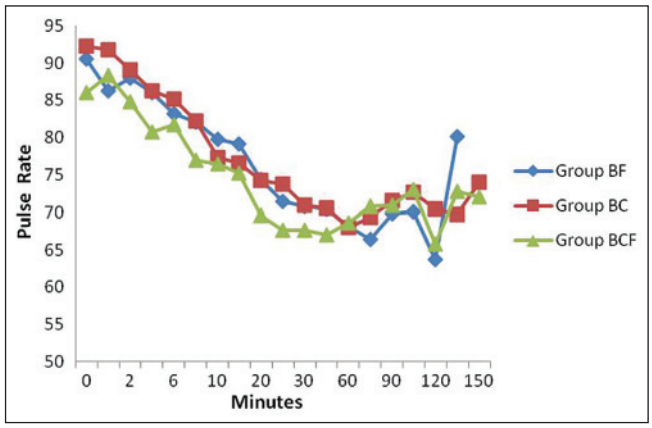


**Figure 1:** Comparison of mean heart rate between groups during the intraoperative period MAP = Mean arterial pressure, Group BF = Intrathecal bupivacaine-fentanyl, Group BC = Intrathecal bupivacaine-clonidine, Group BCF = Intrathecal bupivacaine-clonidine-fentanyl)

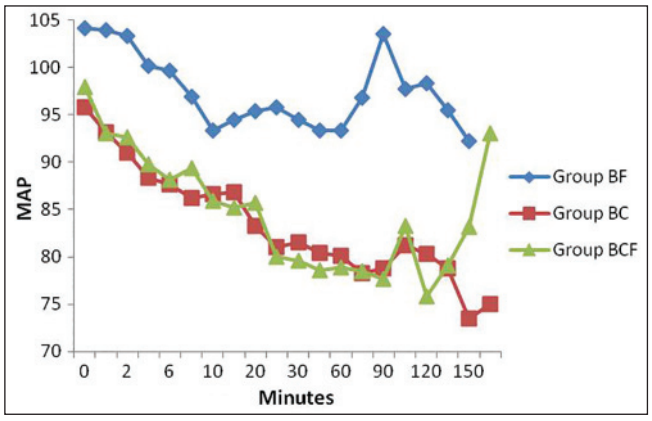


**Figure 2:** Comparison of mean arterial pressure between groups during the intraoperative period (MAP = Mean arterial pressure, Group BF = Intrathecal bupivacaine-fentanyl, Group BC = Intrathecal bupivacaine-clonidine, Group BCF = Intrathecal bupivacaine-clonidine-fentanyl)

We found the dermatomal spread to be more and time of onset of analgesia to be significantly less in patients who were given intrathecal clonidine. Benhamou *et al.*, who compared intrathecal bupivacaine, bupivacaine — clonidine, and bupivacaine — clonidine — fentanyl, also reported a higher spread with the addition of clonidine. They had, however, used a higher dose of clonidine (75 μg) as compared to our study.[3] Dobrydnjov *et al.* reported a higher spread by two to four segments in patients who received 30 μg clonidine with 6 mg bupivacaine, as compared to patients who received 15 μg clonidine with 6 mg bupivacaine or bupivacaine alone for inguinal herniorrhaphy.[5] Heo and Kim *et al.* found no difference in onset between 150 μg clonidine and bupivacaine, as compared to bupivacaine alone, in patients undergoing lower limb or urological operations.[4]

In our study we found that the duration of effective analgesia, duration of sensory and motor block, and time to two-segment regression were significantly more when clonidine was added to bupivacaine and fentanyl. Gautier *et al.* found that patients receiving 30 μg intrathecal clonidine with 2.5 or 5 μg sufentanil had significantly longer lasting analgesia than those receiving 5 μg sufentanil alone (145 ± 36 and 145 ± 43 minutes vs. 104 ± 35).[8] They found that addition of 30 μg clonidine to sufentanil significantly increased the duration of analgesia, as compared to 15 μg clonidine with sufentanil (95 minutes vs. 145 minutes), which produced analgesia comparable to opioid alone in the first stage of labor.[8]

Benhamou *et al.* also found that the duration of analgesia was longer in the BCF group as compared to the BC group (215 ± 79 vs. 183 ± 80 minutes, $P < 0.05$). However, compared to our study the duration of analgesia was much less in both their study groups. This could perhaps be attributed to the lower dose of bupivacaine used by them.[3]

We found the incidence of intraoperative pain and requirement of postoperative analgesics to be significantly less when clonidine was added to bupivacaine alone or to a mixture of bupivacaine and fentanyl, as compared to the group that did not receive clonidine. Benhamou *et al.* also found no significant difference in the incidence of intraoperative pain between the bupivacaine — clonidine and bupivacaine — clonidine — fentanyl groups.

Although we found the time to the first analgesic request to be significantly longer with bupivacaine — clonidine — fentanyl, as compared to bupivacaine — clonidine, there was no significant difference in the total number of analgesics required in the first 24 hours after surgery. Hamid HM and Benhamou *et al.* also found the time to the first analgesic request to be longer in patients who received bupivacaine — clonidine — fentanyl, as compared to those who received bupivacaine — clonidine.[3,12] However, Hamid HM noted a significant decrease in the mean dose of analgesics given in the postoperative period to patients in the bupivacaine — clonidine — fentanyl group.[12] Tuijl *et al.* who compared hyperbaric bupivacaine with bupivacaine — clonidine found that although addition of clonidine prolonged analgesia, it did not reduce the postoperative morphine consumption during the first 24 hours.[13]

We did not note any difference in the hemodynamic profile between the groups. This was perhaps attributed to the preloading done prior to the block. Despite our small sample size, this implied that the intrathecal dose of clonidine studied (30 μg) might not produce significant hemodynamic effects in healthy patients aged between 45 and 65 years. This was in accordance with various other studies.[12] Intrathecal clonidine had a biphasic effect on blood pressure.[14] As clonidine was a mixed α1-α2-adrenergic agonist, it was

associated with a U-shaped hemodynamic dose-response curve.[2] Studies using lower (15 to 30 μg) and higher doses (300 to 450 μg) of intrathecal clonidine found no hemodynamic instability while most of the studies using doses between 45 μg to 150 μg reported significant hypotension and bradycardia.[9,15,16,17]

As far as the incidence of side effects is concerned, we found shivering to be much less in patients given intrathecal clonidine. This is in accordance with a study by Paech *et al*., who too found that clonidine added to bupivacaine and fentanyl for patient-controlled epidural analgesia during labor reduces shivering.[18] In our study we found the incidence of sedation to be the highest with bupivacaine–clonidine and this was followed by the bupivacaine — clonidine — fentanyl and bupivacaine — fentanyl groups. Benhamou *et al*. and Liu *et al*. also found that clonidine caused sedation, and Filos *et al*. demonstrated a dose-dependent sedation in their patients.[3,16,19] Sedation represented an α2-adrenergic effect, as it had been seen that sedation from epidural clonidine could be reversed by a specific antagonist, yohimbine, in postoperative patients.[19] Sedation did not exceed grade 2 in any of our patients and we feel that mild-to-moderate sedation might be a desirable effect in postoperative patients. We did not find pruritus in any of our patients, unlike other studies.[3]

In conclusion we observed that 30 μg of clonidine added to bupivacaine and fentanyl increased the duration of effective analgesia as well as the duration of sensory and motor block, as compared to bupivacaine — clonidine and bupivacaine — fentanyl combinations, without causing any significant hemodynamic side effects. The incidence of intraoperative pain and requirement of postoperative analgesics is significantly less with the addition of clonidine to the intrathecal mixture. One of the limitations of our study was the small sample size. Although certain trends could be established in this pilot study, further controlled, large sample-sized studies are required to confirm the results.

## References


1. Kizilarslan S, Kuvaki B, Onat U, Sağiroğlu E. Epidural fentanyl-bupivacaine compared with clonidine-bupivacaine for analgesia in labour. Eur J Anesthesiol 2000;17:692-7.
2. Chiari A, Lorber C, Eisenach JC,Wildling E, Krenn C, Zavrsky A, *et al*. Analgesic and hemodynamic effects of intrathecal clonidine as the sole analgesic agent during first stage of labor: A dose-response study. Anesthesiology 1999;91:388-96.
3. Benhamou D, Thorin D, Brichant JF, Dailland P, Milon D, Schneider M. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section. Anesth Analg 1998;87:609-13.
4. Heo GJ, Kim YH, Oh JH, Joo JC. Effect of intrathecal clonidine in hyperbaric bupivacaine spinal anesthesia. Korean J Anesthesiol 1997;33:304-8.
5. Dobrydnjov I, Axelsson K, Thörn SE, Matthiesen P, Klockhoff H, Holmström B, *et al*. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: A randomized double-blinded study. Anesth Analg 2003;96:1496-503.
6. Sia AT. Optimal dose of intrathecal clonidine added to sufentanil plus bupivacaine for labour analgesia. Can J Anesth 2000;47:875-80.
7. JuliãoMC, Lauretti GR. Low dose intrathecal clonidine combined with sufentanil as analgesic drugs in abdominal gynecologicalal surgery. J Clin Anesth 2000;12:357-62.
8. Gautier PE, De Kock M, Fanard L, Van Steenberge A, Hody JL. Intrathecal clonidine combined with sufentanil for labor analgesia. Anesthesiology 1998;88:651-6.
9. De Kock M, Gautier P, Fanard L, Hody JL, Lavand'homme P. Intrathecalropivacaine and clonidine for ambulatory knee arthroscopy: A dose-response study. Anesthesiology 2001; 94:574-8.
10. Wilson E, David A, Mackenzie N, Grant IS. Sedation during spinal anesthesia: Comparison of propofol and midazolam. Br J Anesth 1990;64:48-52.
11. Eisenach JC, De Kock M, Klimscha W. Alpha(2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). Anesthesiology 1996;85:655-74.
12. Hadil Magdil Abdel Combined low dose clonidine with fentanyl as an adjuvant to spinal bupivacaine 0.5% for anal surgery. Ain Shams J Anesthesiol 2009;2: Page no. 35-39.
13. van Tuijl I, van Klei WA, van der Werff DB, Kalkman CJ. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after Caesarean section: A randomized controlled trial. Br J Anesth 2006;97:365-70.
14. Eisenach JC, Tong CY. Site of hemodynamic effects of intrathecal alpha2-adrenergic agonists. Anesthesiology 1991;74:766-71.
15. vanTtuijlI, Giezeman MJ, Braithwaite SA, Hennis PJ, Kalkman CJ, van Klei WA. Intrathecal low-dose hyperbaric bupivacaine-clonidine combination in outpatient knee arthroscopy: A randomized controlled trial. Acta Anesthesiol Scand 2008;52:343-9.
16. Filos KS, Goudas LC, Patroni O, Polyzou V. Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose-response study. Anesthesiology 1994;81:591-601.
17. Sethi BS, Samuel M,Sreevastava D. Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine.Indian J Anesth 2007;51:415-9.
18. Paech MJ, Pavy TJ, Orlikowski CE, Evans SF. Patient-controlled epidural analgesia in labor: The addition of clonidine to bupivacaine-fentanyl. Reg Anesth Pain Med 2000;25:34-40.
19. Liu N, Bonnet F, Delaunay L, Kermarec N, D'Honneur G. Partial reversal of the effects ofextradural clonidine by oral yohimbine in postoperative patients. Br J Anesth 1993; 70:515-8.


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