

EFFICACY OF ORAL CLONIDINE AS A PRE-ANAESTHETIC MEDICATION ON THE ANAESTHESIA PROVIDED BY INTRATHECAL BUPIVACAINE WITH FENTANYL

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ABSTRACT

BACKGROUND

Surgical trauma is real and severe tissue damage and pain following surgery is a universal phenomenon. Intrathecally administered narcotics provide selective long duration of analgesia not only in postoperative pain but also in a variety of clinical settings where pain is the predominant feature. Oral clonidine premedication provides preoperative and intraoperative sedation, anxiolysis with intraoperative haemodynamic stability.

MATERIALS AND METHODS

Efficacy of oral clonidine as a pre-anaesthetic medication on the anaesthesia provided by intrathecal bupivacaine with fentanyl. In this study, lumbar subarachnoid injection of hyperbaric bupivacaine 0.5% (15 mg) was given to 120 patients randomly divided into 4 groups (30 each), who had undergone vaginal hysterectomies; 30 patients were given oral placebo premedication with spinal bupivacaine (Group B), 30 patients were given oral placebo premedication and intrathecal fentanyl 10 ug with bupivacaine (Group FB), 30 patients were given oral clonidine 150 ug 90 minutes before subarachnoid block with spinal bupivacaine (Group CB) and another 30 patients were given oral clonidine 150 ug and intrathecal fentanyl 10 ug with bupivacaine (Group CFB).

RESULTS

Oral clonidine premedication prolonged the duration of both sensory (274 + 40.4 mins. vs 184.9 + 18.1 mins. in Group B) and motor blockade (122.8 + 21.3 mins. vs 96.5 + 13.2 mins. in Group B) of bupivacaine. Highest dermatomal levels were achieved with intrathecal fentanyl. Like clonidine, fentanyl itself prolonged the duration of sensory (274.5 + 28.3 mins.) and motor blockade (109 + 20.0 mins.) of bupivacaine. The combination of clonidine and fentanyl with bupivacaine very significantly prolonged the duration of both motor blockade (125.4 + 18.7 mins.) and the total duration of analgesia (357 + 35.4 mins.). The complications associated with clonidine were hypotension, bradycardia and sedation. The complications with fentanyl were nausea, vomiting and pruritus. There was no increased severity of adverse effects with oral clonidine added to intrathecal fentanyl.

CONCLUSION

This study concludes the combination of oral clonidine and intrathecal fentanyl with bupivacaine increased the intraoperative analgesic efficacy and significantly prolonged the postoperative analgesia.

KEYWORDS

Clonidine, Fentanyl, Spinal Bupivacaine, Alpha 2 Agonist.

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BACKGROUND

This study was done after getting approval from Ethical Committee and informed consent of the patients and conducted in the period from Feb 2015 to Oct 2015. Clonidine, an imidazole compound, was synthesised in the early 1960's. It is a selective agonist for alpha-2 receptor with a ratio of 200:1 (alpha-2: alpha-1) and it is a partial agonist. It is rapidly and almost completely absorbed after oral administration and its bioavailability is nearly 100%. Peak plasma concentration is reached within 60 – 90 mins. and maximal hypotensive effects are observed in 1 – 3 hrs. after an oral dose.

The half-life of clonidine is between 6 to 24 hrs. and approximately 50% of the drug is metabolised in the liver to inactive metabolites, while the rest is excreted unchanged by the kidney. It acts on locus coeruleus major site for the hypnotic action of the alpha-2 agonists. High densities of alpha-2 agonist binding sites have been observed in the dorsal motor nucleus of vagus nerve, which may be the site of the bradycardia and hypotensive effects of the alpha-2 agonists. Potent analgesic by itself and act synergistically; clonidine and opioids mediate the analgesic action through independent receptors. Clonidine inhibits noradrenaline release from the peripheral nerve ending and this property in part contributes to the bradycardia effect of this agent. Clonidine has been documented to release Endothelial Derived Relaxant Factor (EDRF) in coronary artery and to enhance coronary blood flow induced by endogenous and exogenous adenosine. Clonidine potentiate the anaesthetic action of other agent, in particular narcotics and local anaesthetics and to reduce anaesthetic requirements during surgery.

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MATERIALS AND METHODS

This is a prospective double-blinded, randomised, placebo-controlled study; 120 patients who were posted for elective gynaecological surgeries (vaginal hysterectomy) were chosen at random. All of them belonged to ASA I and ASA II, age ranging between 24 and 70 years. Patients who had spinal deformities, bleeding disorders, local skin sepsis and chronic pulmonary diseases were excluded from the study. Informed consent was obtained after explaining the procedure in detail. Pre-anaesthetic assessment was done to exclude any local or systemic diseases, which might interface with the anaesthesia. Baseline measurement of pulse rate, respiratory rate, blood pressure and SpO2 were done. Patients were explained about the ten points Visual Analogue Pain Scale (VAPS).

Patients were randomised in a double-blinded fashion to one of four groups. Group B, FB, CB and CFB. In this study lumbar subarachnoid injection of hyperbaric bupivacaine 0.5% (15 mg) was given to 120 patients who had undergone vaginal hysterectomies; 30 patients were given oral placebo premedication with spinal bupivacaine (Group B), 30 patients were given oral placebo premedication and intrathecal fentanyl 10 ug with bupivacaine (Group FB), 30 patients were given oral clonidine 150 ug 90 minutes before subarachnoid block with spinal bupivacaine (Group CB) and another 30 patients were given oral clonidine 150 ug and intrathecal fentanyl 10 ug with bupivacaine (Group CFB).

After explaining the procedure, patients were placed in the right lateral position. After thorough aseptic precautions in L3-L4 interspinous space using a 23-G Quincke point spinal needle, subarachnoid puncture was done through midline approach. After ensuring free flow of cerebrospinal fluid total volume of subarachnoid injection was 3.2 mL in all the four groups. Patients were immediately returned to the supine position after completion of the subarachnoid block. Mean Arterial Pressure (MAP), respiratory rate, pulse rate and SpO2 were monitored every two minutes for the first 20 minutes, then every 10 minutes in the operating room and every 30 minutes in the postoperative recovery room and in the postoperative ward.

Sensory Blockade

The onset of highest dermatomal level and the duration of the sensory block were assessed by pinprick method every 30 seconds for the first 10 minutes and then every 10 minutes after subarachnoid block. The time from the intrathecal injection to the highest sensory level, regression of sensory level by two-segments from the highest sensory level, regression of sensory level by two segments from the highest sensory level were recorded.

VAPS and Quality of Analgesia (Visual Analog Pain Scale)

Duration of absolute pain free period was defined as the time from the intrathecal injection to the perception of mild pain (VAPS = 0 - 1).

The Onset and Duration of Grade 3 Motor Block

It was assessed every 30 secs. for the first 10 minutes and then every 10 minutes after subarachnoid block by Bromage grading. Respiratory rhythm and rate were observed every 10 minutes in the operating room and every 30 minutes in the postoperative room.

Blood Pressure and Pulse Rate

Systolic and diastolic blood pressure by non-invasive method, pulse rate and SpO2 through pulse oximetry was recorded every 10 minutes in the operating room and every 30 minutes thereafter. Episodes of perioperative hypotension (Mean arterial pressure < 70 mmHg), bradycardia (heart rate < 50 beats per minute) and desaturation (SpO2 < 90%) were recorded.

Sedation

Level was assessed every 10 minutes intraoperatively and every 30 minutes in the postoperative room using Brain Ready Sedation Score. Side effects such as nausea and vomiting, pruritus were observed. Intraoperative as well as postoperative incidences of shivering were recorded.

Shivering

Incidence of shivering was recorded intraoperatively. Shivering was graded as (Mao CC et al). None: No perceptible tension of muscles observed; Mild: Slight muscle tonus (masseter muscle); Moderate: Real shivering (proximal muscles); Severe: Generalised shivering (whole body).

Datas were analysed using one-way analysis of variance. P value of < 0.05 was considered statistically significant. Datas are presented as mean + SD, mean values (ranges) and percentages.

RESULTS

Groups	Dermatomal	Mean ± SD
B	T5 - T9	7.3 ± 0.96
FB	T4 - T9	5.9 ± 1.01
CB	T4 - T9	6.7 ± 1.26
CFB	T4 - T9	5.7 ± 1.11

Table 1. Highest Dermatomal Levels

P - value < 0.05.

Groups	Time for Highest Dermatomal Level (Mins.)	Mean ± SD (Mins.)
B	5 - 10	6.9 ± 1.2
FB	4.5 - 9	6.4 ± 1.2
CB	4.5 - 9	6.9 ± 1.3
CFB	4 - 8	6.2 ± 1.2

Table 2. Time for Highest Dermatomal Level (Mins.)

P value > 0.05.

Groups	Time for 2-Segments Regression (Mins.)	Mean ± SD (Mins.)
B	58 - 93	71.9 ± 9.2
FB	68 - 122	94.8 ± 14.2
CB	67 - 144	93.6 ± 11.0
CFB	66 - 140	102.5 ± 14.9

Table 3. Time for 2-Segments Regression (Mins.)

P - value > 0.05.

Groups	Onset of Grade 3 Motor Blockade (Mins.)	Mean ± SD (Mins.)
B	4 - 10	7.1 ± 1.4
FB	4 - 8	6.4 ± 1.1
CB	5 - 9	6.7 ± 1.1
CFB	4.5 - 9	6.4 ± 1.1

Table 4. Onset of Grade 3 Motor Blockade (Mins.)

P - value < 0.05.

Groups	Duration of Grade 3 Motor Blockade (Mins.)	Mean \pm SD (Mins.)
B	66 - 118	96.5 \pm 13.2
FB	85 - 135	109 \pm 20.0
CB	95 - 185	122.8 \pm 21.3
CFB	95 - 174.5	125.4 \pm 18.7

Table 5. Duration of Grade 3 Motor Blockade (Mins.)

P - value > 0.05.

Groups	Duration of Absolute Pain Free Period VAPS = 0 - 1 (Mins.)	Mean (Mins.)
B	115 - 168	138.5 \pm 16.5
FB	163 - 284	206.3 \pm 45.0
CB	140 - 315	214.9 \pm 42.4
CFB	223 - 373	294 \pm 33.7

Table 6. Duration of Absolute Pain Free Period VAPS = 0 - 1 (Mins.)

P - value > 0.05.

Groups	Total Duration of Analgesia VAPS = 5 or More (Mins.)	Mean (Mins.)
B	152 - 223	184.9 \pm 18.1
FB	215 - 359	274.5 \pm 28.3
CB	180 - 378	274 \pm 40.4
CFB	268 - 423	357.1 \pm 35.4

Table 7. Total Duration of Analgesia VAPS = 5 or More (Mins.)

P - value > 0.05.

Groups	Hypotension (No. of Patients)	Nausea and Vomiting	Pruritus	Shivering
B	2	-	-	5
FB	3	3	2	4
CB	5	-	-	-
CFB	7	4	3	-

Table 8. Complications

DISCUSSION

Prolongation of the local anaesthetic blockade has been attributed to localised vasoconstriction, thereby decreasing the uptake of local anaesthetics from the spinal subarachnoid space.¹ (Maddi R, Francis D et al) Recent studies evaluate the role of Alpha₂-adrenergic agonist in modulating neural pathways and demonstrate that these drugs inhibit in vitro nerve conduction in A and C fibres. Clonidine enhances the effects of lidocaine on C-fibre action potential. Clonidine is also effective after oral administration reaching a peak plasma concentration within 60 - 90 mins. When administered as a pre-anaesthetic medication clonidine provides preoperative sedation, greater intraoperative haemodynamic stability and a reduction in the anaesthetic and postoperative analgesic requirements. Prolongation of local anaesthetic-induced spinal sensory and motor block is well documented after co-administration with intrathecal-clonidine² and also by orally clonidine 60 - 90 minutes before subarachnoid block with local anaesthetics (Bonnet F et al).

Postoperative pain relief following intrathecal bupivacaine was prolonged by both oral clonidine as well as intrathecal

clonidine.³ (Dobrydnjov I Axelsson K et al). Oral clonidine attains a peak plasma concentration 60 - 90 minutes after administration has potent antinociceptive action through Alpha₂ receptor mediated mechanism in the dorsal horn of spinal cord and blocks the conduction in A ∞ and C fibres.

Hunt Co, Naulty et al, intrathecal fentanyl has also been reported to improve intraoperative analgesia and to prolong the duration of bupivacaine induced spinal block.⁴ Wang C, Chakrabarti MK, Whitwam JG. Recently, studies⁵ also demonstrated that intrathecal fentanyl acts synergistically to enhance the effect of bupivacaine on afferent nociceptive pathways in dogs.

The combination of clonidine with fentanyl increased the intraoperative analgesic efficacy and significantly prolonged postoperative analgesia compared with clonidine alone. Experimental studies have shown that synergism can be demonstrated between intrathecal opioids and alpha₂ agonist. Highest dermatomal levels achieved was significantly different from Groups B and FB, Group B and CFB (P value < 0.05). So with fentanyl added to with bupivacaine, the dermatomal level after intrathecal injection was found to be higher. There was no significant difference between Groups B and CB. No significant spread of sensory block was observed in oral clonidine with bupivacaine group. The high dermatomal level in CFB was attributable to the fentanyl.

The two-segment regression time was significantly different between Groups B and CFB, CB and CFB. B and FB, B and CB (P value < 0.05). No significant difference between Groups FB (94.8 \pm 14.2) and CB (93.6 \pm 11.6). The two-segment regression time was prolonged significantly both in fentanyl with bupivacaine and clonidine with bupivacaine. If both added together as in CFB, the regression time was still more prolonged 102.5 \pm 14.9 mins. The results of this study correlates well with a similar study reported by⁽³⁾ (Dobrydnjov I and Axelsson) that the two-segment regression time was significantly longer in the clonidine group.

Significant difference among groups in duration of Grade 3 motor blockade (P value of < 0.05). The duration of motor blockade was significantly prolonged in clonidine pre-medicated Groups (CB and CFB). The results are well-correlated with similar study⁽⁶⁾ Harbhej Singh et al. He had demonstrated that oral clonidine prolonged the duration of Grade 3 motor blockade of spinal tetracaine and also oral clonidine prolonged the duration of motor block by lidocaine,⁷ Liu S and Chiu et al.

There was significant difference (P < 0.05) in the duration of absolute pain free period between Groups FB, 206.3 \pm 45 mins. and CB 214.9 \pm 42.4 mins.

There was significant difference in total duration of analgesia between groups except between Groups FB and CB (P value of < 0.05). The duration was almost similar in both FB and CB Groups. The duration is very significantly prolonged in Group CFB. Similar studies about postoperative pain relief following intrathecal bupivacaine (15 mg) combined with oral clonidine (150 μ g) and observed that oral clonidine prolonged the time until the first request for analgesics, 313 \pm 29 mins. versus 236 \pm 27 mins. in bupivacaine-only group. No shivering was seen in clonidine premedicated patients,⁸ Mao CC et al.

CONCLUSION

This study demonstrates that oral clonidine premedication prolonged the duration of sensory and motor blockade of

intrathecal bupivacaine. Intrathecal fentanyl itself prolonged the sensory blockade of bupivacaine. The combination of oral clonidine and intrathecal fentanyl with bupivacaine increased the intraoperative analgesia efficacy and significantly prolonged postoperative analgesia compared with either clonidine or fentanyl alone. However, this combination was associated with slightly increased incidence of bradycardia and hypotension which were easily treatable and moderately increased sedation, which can be considered an advantageous side effects because it allows a calm intraoperative course.

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