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THE COMPARISON OF THE ANALGESIC EFFECT OF INTRAINCISIONAL KETAMINE OR CLONIDINE ADMINISTRATION WITH BUPIVACAINE AFTER CAESAREAN SECTION UNDER SPINAL ANAESTHESIA: A RANDOMIZED, DOUBLE BLIND, COMPARATIVE STUDY.

Anesthesiology

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ABSTRACT

Back ground and Aim: Pain is a sensational and emotional experience due to tissue injury .The main aim for post-caesarean section analgesia are to provide adequate pain relief, encourage early ambulation, and minimize side-effect in both the mother and the baby.

This study was aimed to evaluate the clinical efficacy of subcutaneous injection of ketamine or clonidine along with bupivacaine at the incision site to reduce caesarean section pain.

Method: Fifty patients, aged between 20 and 35 years old, scheduled for elective caesarean section, under spinal anaesthesia were enrolled to this double-blind, randomized, comparative study. Patients were divided into two groups of 25 patients in each group. Group-K (n=25): received 50 mg of ketamine added to 20ml of 0.25% of bupivacaine subcutaneously in the incision site .Group C (n=25): received 75µg of clonidine added to 20ml of 0.25% of bupivacaine.

The first analgesic request, the pain intensity score, sedation score and adverse effects were evaluated for 24 hours.

Statistical analysis- The quantitative data was analyzed by applying one way -ANOVA and post hoc test –Tuckey for the intergroup comparison. Chi-Square test or Kruskal-Wallis test was used for the analysis of qualitative data.

Results: The first time analgesic requested was longer in clonidine group as compared to ketamine group. ($P < 0.05$). VAS score was significantly lower in groups C as compared to group K ($P < 0.05$).

Conclusions: Patients who received clonidine with bupivacaine after caesarean section subcutaneously at incision site had lower pain intensity and longer total duration of analgesia in comparison to ketamine without any significant side effects.

KEYWORDS

Ketamine; clonidine, Caesarean Section, postoperative Pain

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Postoperative pain is defined as a condition of tissue injury together with muscle spasm after surgery. It has been shown that the use of analgesic drugs reduces the postoperative complications, however in most cases the pain is not controlled adequately. [1-3] Pain after cesarean section can hinder mother's ability for her and newborn's care. Postoperative complications especially risk of thromboembolic disease which already increase during pregnancy are further increased due to immobility caused by postoperative pain.

Severe acute post cesarean delivery pain is associated with persistent pain and postpartum depression for eight weeks after delivery.[4-5]

Sensitization of spinal cord by activation of glutamate and aspartate in N-Methyl-D-aspartate (NMDA) receptors results in pain transmission. [6] Recognition of NMDA receptors and the roles they play in reducing the patients' pain cause a novel evolution in consumption of such receptor antagonists like ketamine. [7-9] Using low-dose ketamine as the antagonist of NMDA receptors not only alleviate the patient's pain but also lessen their needs for systemic opioid.[10]

Clonidine, a α2-adrenoceptor agonist, has potent antinociceptive properties. A peripheral analgesic action of clonidine has been suggested after topical application in the treatment of sympathetic pain [14] and after intra-articular administration in preclinical [15] and clinical studies. Though, the precise mechanism of topical clonidine analgesia remains unclear, it has been suggested that sympathetic neural activity and norepinephrine have an excitatory effect on nociceptive discharge after cutaneous injury.[16] Clonidine inhibits the release of norepinephrine from prejunctional α2-adrenoreceptors in the periphery, it may potentially inhibit neural activity in nociceptive pathways.[17] Other proposed mechanisms include enhancing the effect of local anaesthetics by selectively blocking conduction of A delta and C fibres, and release of enkephalin like substances which produce a peripheral analgesic effect.[18]

Few studies have used clonidine infiltration at the surgical site with conflicting results. [19-23] Pre-incisional injection of clonidine with ropivacaine in the tonsillar fossae was found to be effective in decreasing postoperative analgesic consumption and pain scores.[19] However, in another study, clonidine administration with bupivacaine in wound infiltration did not improve postoperative analgesia obtained by bupivacaine alone for elective inguinal hernia repair.[22]

Therefore we have conducted this study to evaluate and compare the analgesic efficacy of ketamine and clonidine in wound infiltration with bupivacaine in the patients undergoing LSCS. None of the study has compared both the drugs simultaneously.

Subject and Methods

This prospective, randomized, double blind, comparative study was done at Sawai Man Singh Medical College, Jaipur after approval by institutional ethical committee. Study was done in 50 patients of ASA grade I, II aged between 20-35 years scheduled for elective lower segment caesarean section under sub arachnoid block. Patients with any contraindication to spinal anaesthesia or major systemic illness were excluded from the study.

After thorough pre anaesthetic examination day before surgery, patients were kept nil by mouth over-night, informed written consent was taken and checked.

Patients were randomized by sealed envelope method in two groups

Group-K (n=25): 50 mg of ketamine added to 20ml of 0.25% of bupivacaine.

Group C (n=25): 75µg of clonidine added to 20ml of 0.25% of bupivacaine.

The procedure was explained to the patients and a written informed consent for spinal anesthesia and operation was taken. Concept of VAS

score was explained to the patient in the pre-operative area on the day of the surgery.

Patient was taken to the OT, fasting status was confirmed, monitors was attached to the patient; base line HR, SBP, DBP, MAP, and SpO2 was recorded. A good IV line was secured with 18G cannula and Inj. Ranitidine (50mg) &Inj. Metoclopramide (10mg) was given intravenously. Hydration was consists of 15ml/kg Ringer lactate solution preoperatively and 10ml/kg/hr after spinal anesthesia. Under all aseptic precautions spinal anesthesia was performed at the $L_3 - L_4$ interspace, with the patient in sitting position. Inj. bupivacainr 0.5% heavy 2 ml was injected over 30 seconds through a 25-gauge spinal needle. Patient was placed in supine position with head down tilt immediately after spinal injection to achieve level of block of T5-T6. Oxygen (4L/min) was administered via a ventimask..

Vitals were checked every 2 minutes for 10 minutes and after that every 5 minutes till the end of the surgery.

At the end of the surgery after the closure of rectus sheath, study drug was given subcutaneously in the incision site and time and vital parameters noted.

Hypotension, defined as a decrease of systolic blood pressure by more than 30% from baseline or a fall below 90 mmHg, was treated with incremental IV doses of mephentermine 5 mg and IV fluid as required. Bradycardia, defined as heart rate < 50 bpm, was treated with IV atropine 0.6 mg.

Postoperatively, the pain assessed by using visual analogue pain scale (VAS) between 0 and10 (0 = no pain, 10 = most severe pain).It was assessed at every 30 min. Patients allowed to receive rescue analgesic on VAS score of 3.

Intravenous Inj. Diclofenac (75 mg) was given as rescue analgesic. Time from the study drug administration in the incision site to the first administration of rescue analgesic (total duration of analgesia) noted. This was the end point of our study. Patient was monitored for 24hrs for any adverse effects.

Postoperative sedation level was noted according to the "Four-Point Sedation Scale". Complications such as nausea, vomiting, hypotension; bradycardia, and hallucination were noted and managed accordingly.

Statistical Analysis

The sample size of the study was calculated as 20 subjects in each of the two groups with an alpha error of 0.05 and power of 90% assuming difference of means of time to first rescue analgesia to be 48 ± 45min according to the pilot study. For the study purpose we have taken total of 50 patients with 25 patients in each group. (n=25)

The data of continuous (quantitative) variables was presented in terms of mean and standard deviation and the categorical (qualitative) variables were expressed in frequency and percentage. The quantitative data was analyzed by applying one way -ANOVA and post hoc test –Tuckey for the intergroup comparison. Chi-Square test or Kruskal-Wallis test was used for the analysis of qualitative data. A P value of <0.05 was considered statistically significant.

Result

Spinal anesthesia was successful in all patients, and all patients completed the study. All groups were comparable with respect to age, weight, height, ASA status, and duration of surgery. There were no statistically significant differences in the demographic characteristics between the groups (Table :1) ($P > 0.05$)

Time for first dose of rescue analgesia was more in clonidine group 265.28±20.737 min. when compared with ketamine group 204.12±32.303 min. It was stastically significant. ($P < 0$). (Table: 2)

There was no significant difference between the mean HR and MAP in clonidine group and ketamine group throughout the post-operative period. None of the patient had bradycardia in both the groups. Only two patients had hypotension in clonidine group which was managed by IV fluids only. It was statistically nonsignificant ($P > 0.05$). Two patients in ketamine group had nausea and vomiting and two patients were found sedated. It was statistically not significant ($P > 0.05$) (Table: 3).

The VAS scores were lower in clonidine group compared to ketamine group at different time interval. (Figure: 1)

Discussion

Surgical wound infiltration with local anaesthetic agents is a cost-effective and relatively low-risk method for providing postoperative analgesia after surgery. The duration of analgesia can be prolonged by addition of various adjuvants such as epinephrine, ketorolac, α2-adrenoceptor agonist and an opioid.

In the present study, patients who received clonidine in wound infiltration with bupivacaine had longer total duration of analgesia and reduced postoperative VAS scores as compared to ketamine infiltration with bupivacaine. Patients were hemodynamically stable and had very few side effects. (P>0.05) Similar results were observed in a study done by MS Nataraj and colleagues [23]. Patients received 3 µg/kg clonidine mixed with 0.25% bupivacaine 30 ml for wound infiltration after caesarean section. Time for first request of analgesia was prolonged in clonidine as compared to control group ($P < 0.0001$), total tramadol consumption was significantly less and pain scores were lower in clonidine group up to 12 h.

In a study done by N. Bharti et al[21]. patients received either 3 ug/ kg of clonidine intravenously plus wound infiltration with 30 ml of 0.25% bupivacaine or wound infiltration with 3 ug /kg clonidine with 30 ml of 0.25% bupivacaine after open cholecystectomy. In their study, patients who received clonidine either in wound infiltration with bupivacaine or by i.v. route had reduced postoperative pain scores and morphine requirement compared to the control group. The incidence of hypotension and sedation was less in patients who received clonidine for wound infiltration.

Giannoni et al.[19]found that peritosillar infiltration of clonidine 1 ug /kg along with ropivacaine significantly reduced the requirement of postoperative analgesics (P<0.05). Patients who received clonidine with ropivacaine had lower pain scores.

Connelly et al [20]in their study used clonidine in the dose of 0.5 ug /kg in patients undergoing inguinal hernia repair under monitored anaesthesia care. They found only 2 hours prolongation in postoperative analgesia after surgical site infiltration or i.m. administration. The authors said that higher concentrations of clonidine (>.0.5 µg/ kg) may be required to enhance the analgesic effect.

Behaeen K et al [10] studied the analgesic effect of subcutaneous infiltration of low dose ketamine before and after cesarean section. The results showed that Patients who were given ketamine before or after cesarean section subcutaneously at the incision site had lower pain intensity and less analgesic consumption than patients who were given placebo.

New research has shown that ketamine has a local analgesic effect. [12] Adding ketamine to local anesthetics or other analgesic drugs and their administration around peripheral nerves or in spinal space has improved the analgesia and prolonged the duration of the reduced pain. [13] Local use of ketamine - aiming to affect peripheral receptors - can reduce the possible side effects such as psychological reactions and sedation.

Kwok et al. [11] found that the preincision administration of low dose intravenous ketamine (0.15 mg/kg) in gynecologic laparoscopic surgery was more effective concerning post-operative pain and first analgesic request time rather than post-surgical administration.

The limitation of our study is that we could not calculate the 24 hours analgesic consumption and the patients were followed-up for first 24 hours only.

Conclusion: clonidine when administered in wound infiltration with bupivacaine provides effective postoperative analgesia with fewer side-effects. Therefore, clonidine with bupivacaine can be used for surgical site infiltration as part of a multimodal analgesia technique.

Table:- 1 Demographic profile

VARIABLES	GROUP-K	GROUP-C	P VALUE
AGE	27.2±4.582	28.48±4.154	0.306
WEIGHT	65.84±8.279	69.04±8.909	0.194
HEIGHT	159.64±7.239	162.6±7.041	0.149
ASA GRADE (I:II)	20:5	21:4	0.6
DURATION	56.04±13.510	55.44±12.271	0.87

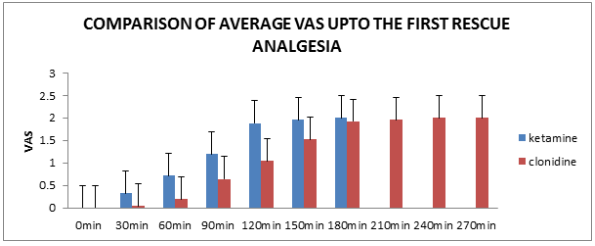
Table:-2 Analgesic Duration

VARIABLES	GROUP-K	GROUP-C	P VALUE
TIME TO FIRST RESCUE ANALGESIA (min)	204.12±32.303	265.28±20.737	0

Table--3 Adverse Effects

VARIABLES	GROUP-K	GROUP-C	P VALUE
SEDATION	2	0	0.47
NAUSEA & VOMITING	2	0	0.47
HYPOTENSION	0	2	0.47
BRADYCARDIA	0	0	1
HALLUCINATION	0	0	1

Figure:-1



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