The Evaluation of Bupivacaine-Clonidine Combination Effect Intrathecally for Postoperative Analgesia and Motor Block in Caesarean Section Patient

Abdulmutaleb B. Issa,* Masoud A. Elfeituri,** Ahmed M. Gellai,**

Abstract:

Background: During the last two decades, alpha-2 agonists such as clonidine have been used neuroaxially as LA adjuncts to improve and prolong the quality of postoperative analgesia in caesarean section patient.

Objective: the aim of this prospective observational study was to assess the effectiveness of administration of clonidine in combination with heavy bupivacaine intrathecally in management of postoperative pain in caesarean section patients.

Methods: In this prospective, randomized single-blinded study after obtaining their informed consent, 68 patients, undergoing caesarean section under spinal anaesthesia, grouped in two groups, 36 pregnant women received intrathecally combination of 2 ml heavy bupivacaine with 50 µg clonidine in 0.5 ml normal saline, using 10 scaled VAS for assessment postoperative pain and bromage score for motor block.

Results: there was a clear difference between the two groups, the duration of sensory block; motor block and analgesia were greatest in first group who received heavy bupivacaine-clonidine combination in comparison with other group that received bupivacaine-fentanyl.

Conclusions: Administration of clonidine to LA intrathecally in caesarean section patient improved the quality of intraoperative sensory block and prolongs the postoperative sensory block, motor block and analgesia.

Key Words: Obstetric, caesarean section, spinal anaesthesia, postoperative pain, bupivacaine, clonidine, fentanyl.

Introduction:

Pain is the most symptom that brings patient to a physician either due to pathological process or in postoperative period, for that any treatment plan must be directed at the underlying process and as well as at controlling pain.

Adequate postoperative pain management is very important issue in postoperative care especially in obstetric patients, inappropriate pain control may lead to increase postoperative morbidity and mortality in addition to other adverse effects like patient's discomfort, infection (immune suppression), delayed mobilization, pulmonary and cardiac complications and thromboembolic complication.

Although several advances have been made in the understanding of pain physiology and the implementation of new analgesics and techniques, many patients still suffer moderate to severe pain.

In our obstetrics' anesthesia department TMC, many studies have been performed to control the postoperative pain in the caesarean section. Patients include epidural analgesia, paracetamol alone or in combination with other analgesics like opioid.

Although, intrathecally bupivacaine-clonidine combination has been used abroad in many universities and hospital, this is the first time that this combination is being used in Libyan obstetric patients. Therefore, assessment of the influence of that combination on clinical functions using 1o scored VAS and Bromage score for assessment postoperative operative pain management and motor block respectively are more objective and adequate.

Bupivacaine:

USES Bupivacaine is used as a local anaesthetic.

Chemical: An amide, which is a structural homologue of mepivacaine.

*) Department of Anaesthesia. Tripoli Medical Center, Tripoli, Libya.

**) Department of Anaesthesia, Faculty of Medicine, University of Benghazi, Benghazi. Libya.

Presentation: As a clear, colourless solution containing 0.25/0.5% bupivacaine hydrochloride – the 0.25/0.5% solutions are available. A 0.5% ('heavy') solution containing 80 mg/ml of glucose (with a specific gravity of 1.026) is also available.

Anaesthetic. Local **Main Action**
Mode of action: LA diffuse in their uncharged base form through neural sheaths and the axonal membrane to the internal surface of cell membrane sodium ion channels. They combined with hydrogen ions to from a cationic species, which enters the internal opening of the sodium ion channel and combined with a receptor. It produces blockade of the sodium ion channel, thereby decreasing sodium ion conductance and preventing depolarization of the membrane.

Routes of administration /doses:
Bupivacaine may be administered topically, by infiltration, intrathecally or epidurally; the toxic dose of bupivacaine is 2 mg/kg (with or without adrenaline). The drug acts within 10-20 minutes and has aduration of action of 4-6 hours.

Systemic Effects:
CVS: Bupivacaine is markedly cardiotoxic. It binds specifically to myocardial proteins. In toxic concentrations, the drug decreases the peripheral vascular resistance and myocardial contractility. It produces hypotension and possibly cardiovascular collapse.

CNS: The principal effect of bupivacaine is reversible neural blockade. This leads to acharacteristically biphasic effect in the central nervous system. Initially, excitation (lightheadedness, dizziness, visual and auditory disturbances and fitting) occurs, increasing doses, depression of both facilitatory and inhibitory pathways occur, leading to central nervous system depression (drowsiness, disorientation and coma). Local anaesthetic agents block neuromuscular transmission when administered intrathecally; it is thought that acomplex of neurotransmitter, receptor and local anaesthetic is formed which has negligible conductance.
Toxicity/ side effects: Allergic reactions to the amide-type local anaesthetic agents are extremely rare. The side effects are predominatly correlated with excessive plasma concentrations of the drug, as described above.

The use of the drug for intravenous regional blocked is no longer recommended, as refractory cardiac depression leading to death has been reported when it is used for this purpose.

Pharmacokinetic:
Absorption: depends on:
1. The site of injection (intercostals>epidural > brachial plexus > subcutaneous).
2. The dose – a linear relationship exists between the total dose and the peak blood concentrations achieved and absorption of local anaesthetic agents is related to:
3. The presence of vasoconstrictors, which delay absorption. The addition of adrenaline to bupivacaine solutions does not influence the rate of systemic absorption as
1. The drug is highly lipid soluble and therefore uptake into fat is rapid and
2. The drug has direct vasodilatory effect.

Distribution Bupivacaine is 95% protein-bound in the plasma; the Vd is 41-103l.

Metabolism: Occurs in the liver by N-dealkylation, primarily to 4. hydroxyl bupivacaine are also formed.
Pipcolyloxylidine. N-desbutyl bupivacaine and
Excretion: 5% of the dose is excreted in urine as pipcolyloxylidine, 16% is excreted unchanged. The clearance is 0.47 l/min and the elimination half-life (after intravenous administration) is 0.31-0.16 hours.

Special Points: The onset and duration of conduction blockade is related to the pKa, lipid solubility and extent of protein binding of the drug. A low pKa and high lipind solubility are associated with a rapid onset time; a degree of protein binding is associated with a long duration of action.

The pKa of bupivacaine is 8.1 and the heptane: buffer partition coefficient is 27.5 in infants under 6 months of age, the low level of albumin and alpha –l-acid glycoprotein results in an increase in the free fraction of bupivacaine. Local anaesthetic agents significantrly increase the duration of action of both levobupivacaine which is a S(-) enantiomer of racemic bupivacaine, which differs in having less CNS and CVS toxicity and less prolonged motor blockade but longer sensory blockade after epidural administration.

Clonidine:

Uses: clonidine is used in the treatment of:

1. All grades of essential and secondary hypertension
2. Hypertensive crises and in the management of
3. Migraine
4. Menopausal flushing and may be of use in
5. Chronic pain
6. During opiate and alcohol withdrawal and
7. for intravenous regional analgesia for chronic regional pain syndromes
8. As LA adjuncts for spinal and epidural anesthesia.

Chemical: An aniline derivative.

Presentation: As 0.1/0.25/0.3 mg tablets and as a clear, colourless solution for injection containing 0.15 mg/ml of clonidine hydrochloride.

Main Action: Antihypertensive, analgesic, sedative and anxiolytic.

Mode of Action: Clonidine acts acutely by stimulating alpha-2 (pre-synaptic) adrenoceptors, thereby decreasing noradrenaline release from sympathetic nerve terminals and consequently decreasing sympathetic tone, it also increases vagal tone. The drug acts chronically by reducing the responsiveness of peripheral vessels to vascoactive substances and to sympathetic stimulation. It has also agonist effects at central imidazoline (I) receptor and some effects on alpha I receptor (I: II >200:1). The analgesic effects are also mediated by activation of alpha-2 adrenoceptors in the dorsal horn of the spinal cord.

Routes of administration/doses:

The adult oral dose is 50-600µg 8.hourly. The corresponding intravenous dose is 0.15-0.3 mg. **When** administered by the epidural route, a dose of 0.15 mg has been used. By spinal route, a dose of 1-1.5µg\kg, the drug acts within 10 minutes and lasts for 3-7 hours when administered intravenously.

Effects:

CVS: When administered intravenously, clonidine causes a transient increase in the blood pressure (due to stimulation of the vascular alpha receptors) followed by a sustained decrease. The HR and Venous return may decrease slightly. The durg has no effect on cardiac contractility and cardiac output is well maintained. The coronary vascular resistance is decreased by clonidine. The SVR is decreased with long-term treatment.

CNS: Clonidine decreases cerebral blood flow and intraocular pressure. It exerts a depressant effect on both spontaneous sympathetic outflow and afferent a delta and C-fiber-mediated somatosympathetic reflexes.

As Clonidine decreases gastric and small bowel motility and is an antisialogogue.

GU: Clonidine reduces renovascular resistance; however, little alteration in the glomerular filtration rate occurs.

Metabolic/Other: The drug causes a decrease in plasma and CNS catecholamine but baroreceptor reflexes are preserved, pressure response to ephedrine or phenylephrine is exaggerated. It also decreases the plasma rennin activity. Blood sugar may be increase secondary to alpha adrenergic stimulation.

Toxicity/Side Effects: drowsiness and a dry mouth may occur in about 50% of patients who receive the drug. Central nervous system disturbances, fluid retention, impotence and constipation have also been reported. Rapid withdrawal of the drug may lead to life-threatening rebound hypertension and tachycardia.

Pharmacokinetic:

Absorption: The drug is rapidly and well absorbed when administered orally, the oral bioavailability is 100%.

Distribution: Clonidine is very lipid-soluble and penetrates the central nervous system. The drug is 20% protein – bound in the plasma, the VD is 1.7-2.5l/kg.

Metabolism: less than half of an administered is metabolized in the liver to inactive metabolites.

Excretion 65% of the dose of clonidine is excreted unchanged in the urine, some 20% is excreted in the faeces. The clearance is 1.9-4.3ml/kg/min and the elimination half-life is 6-12 hours. The latter is markedly increased in the presence of renal impairment; the dose of ml/min.

Special points; clonidine decreases the MAC of **co**-administered volatile. It decreases the incidence of post-anaesthetic shivering and postoperative

Nausea and vomiting. Clonidine decreases the dose of propofal needed for LMA insertion.

Clonidine decreases post-operative agitation in children undergoing sevoflurane anaesthesia.

It prolongs the duration of local anesthesia when co-administered intrathecally and retro

bulbar blocked. The drug is not removed by haemodialysis.

Fentanyl:

Uses of fentanyl:

1. To provide the analgesic component of general anaesthesia
2. In combination with a major tranquillizer to produce neuroleptanalgesia
3. In premedication and has been used
4. for palliative care.

Chemical: A tertiary amine which is a synthetic phenylpiperidine derivative.

Presentation: As a clear, colorless solution for injection containing 50μg/ml of intranasal fentanyl citrate transdrmal patches which deliver 25/50/75/100 mg/hour over a 72-hour period and 200/ 400/ 600/ 800/ 1200/ 1600 mg lozenges.

Main Actions:

Analgesia and respiratory depression.

Mode of Action: Fentanyl is a highly selective mu agonist; the mu-opioid receptor appears to be specifically involved in the mediation of analgesia. Opioids appear to exert their effects by increasing intracellular calcium concentration, which in turn increases potassium conductance and hyperpolarisation of excitable cell membranes. The decrease in membrane excitability that results may decrease both pre- and post-synaptic responses.

Routs of administration /doses:

The adult dose for premedication by the intramuscular route is 50-100 mg. For the induction or supplementation of general anaesthesia, an intravenous dose of 1-100 mg/kg may be used. Fentanyl may also be administered via the epidural route; a dose of 50-100 mg is usually employed. The drug acts in 2-5 minutes when administered intravenously; a small dose has a duration of action of 30-60 minutes, whereas high (>50 mg/kg) doses may be effective for 4-6 hours.

Effects:

CVS: The most significant cardiovascular effect that fentanyl demonstrates is bradycardia of vagal origin; cardiac output, mean arterial pressure, pulmonary and systemic vascular resistance and pulmonary capillary wedge pressure are unaffected by administration of the drug. Fentanyl obtunds the cardiovascular responses to laryngoscopy and intubation.

RS: Fentanyl is a potent respiratory depressant, causing a decrease in both the respiratory rate and tidal volume. It also dimishes the ventilatory response to hypoxia and hyper-capnia. The drug is a potent antitussive agent. Chest wall rigidity (the 'wooden chest ' phenomenon) may occur after the drug on mu receptors located on GABA-ergic interneurons. Fentanyl causes minimal release of histamine; bronchospasm is thus rarely precipitated by the drug.

CNS: Fentanyl is 50-80 times more potent as an analgesic than morphine and has little hypnotic or sedative activity.

There have been several reports of seizure-like motor activity occurring in patients receiving fentanyl; however, no epileptic spike-wave patterns are demonstrable on the EEC (although beta-activity is initially decreased and alpha-activity is increased; subsequently alpha – activity disappears and delta-activity predominates).

GIT: Fentanyl decreases gastrointestinal motility and decreases gastric acid secretion. It also doubles the common bile duct pressure by causing spasm of the sphincter of Oddi.

GU: The drug increases the tone of the ureters, bladder detrusor muscle and vesicular sphincter.

Metabolic/Other: High doses of fentanyl will obtund the metabolic 'stress response' to surgery although the drug has no effect on white cell function. Unlike morphine, fentanyl does not increase the activity of antidiuretic hormone.

Toxicity/Side Effects: Respiratory depression may occur post-operatively, possibly related to the appearance of a secondary peak in the plasma fentanyl concentration due to elution from muscle, vomiting and dependence may also complicate the use of the drug.

Pharmacokinetic:

There is a large interindividual variability in pharmacokinetics.

Absorption: Fentanyl is absorbed orally and has a bioavailability by this route about 33%. Transdermal delivery produces 47% absorption at 24 hours, 88% at 48 hours and 94% by 72 hours.

Distribution: The drug is 81-94% protein-bound in the plasma; the Vd is 0.88-4.41 l/kg. The short duration of action of a single dose of the drug is Due to redistribution, rather than to metabolism (cf. thiopentone).

Fentanyl is more lipid-soluble than morphine and thus crosses the blood-brain barrier more easily; it thus has a more rapid onset of action than morphine.

Metabolism: Fentanyl appears to be metabolized primarily by N-dealklation to norfentanyl with subsequent hydroxylation of this and the parent compound to hydroxypropionyl derivatives. The drug may also undergo hydroxylation and amide hydrolysis. Cytochrome P-450 3A4 plays the predominant role in fentanyl metabolism. As well as the liver, this is also found in human intestine. Some entero-systemic cycling of the drug may occur and first-pass metabolism occurs. The metabolites do not have appreciable analgesic activity.

Excretion: 10% of an administered dose is excreted in the urine .

The clearance is 0.4-1.5 l/min and the elimination half-life is 1.5-6 hours.

Halothane decreases the clearance of fentanyl by 48%, a similar effect occurs with enflurane. The clearance of fentanyl is increased in surgical patients with renal impairment and decreased in patients with hepatic impairment.

Special points:

Fentanyl decreases the apparent MAC of co-administered volatile agents and increases the effect of non-depolarising muscle relaxants to a similar extent as doe's halothane. The drug is pharmaceutically incompatible with thiopentone and methohexitone.

It is unknown whether fentanyl is removed by heamodialysis.

Patients and Methods:

In this prospective study after obtaining their informed consent, sixty eight patients,ASA I ,aged 20-45 yrs undergoing caesarean section under spinal anaesthesia were grouped in two groups.

Group 1(study group): Patients received 2ml of heavy bupivacaine plus 50µg clonidine in 0.5 ns intrathecally.

Group 2(control group): Patients received 2ml of heavy bupivacaine plus fentanyl 20 µg intrathecally.

Patients were preloaded with 10 ml normal saline, then in sitting positions the spinal needle (quincke) 27G inserted at L3-4 with bevel pointed upward and the injectate volume was injected over 20 seconds, then immediately the patients were positioned in supine position.

ECG, blood pressure, O2 sat were measured and recorded before the block, then every 5 minutes after the block for the first 30 minutes then every 10 until the end of the surgery.

After the end of the surgery, every patient was evaluated hourly for sensory block, analgesia and motor block.

10 scored visual analogue scale (VAS) has been used for pain assessment and Bromage scale for motor block.

Result:

Patient demographic data were analyzed by using SPSS TEST for comparison between study and control groups. Data are presented as mean and standard deviation.

A total number of 66 patients enrolled in this study, demographic characteristics of pregnant were parity, age, indication, postoperative pain and motor block post spinal anaesthesia.

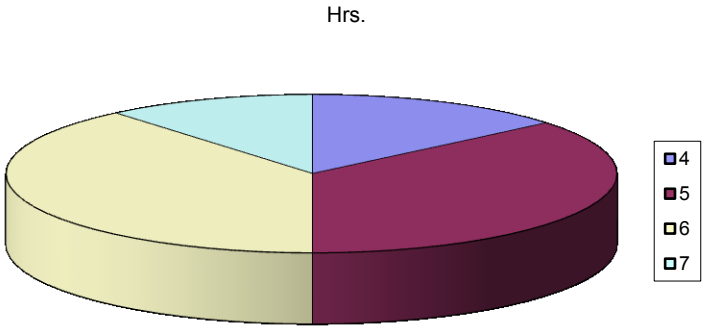
The result for postoperative pain control in (study group1) with heavy bupivacaine and clonidine was mean=5.47hr ±SD=0.88, from those 36 patients, 5 patients (13.9%) were asked for analgesia after 4hrs, 13 patients (36.1%) after 5hrs, 14 patients (38.9%) after 6hrs and 4 patients (11.1%) after 7hrs.compared to (control group 2) with heavy bupivacaine and fentanyl was mean=2.56hrs ±SD0.65, where 1patient (2.8%) was asked for analgesia after 1hr, 16 (44.4%) after 2hrs, 17 (47.2%) after 3hrs and 2 (5.6%) after 4hrs.

The result for motor block in (study group 1) was mean=4.14hrs±SD0.59, where 4 patients (11.1%) had got free movement in their lower limbs after 3hrs, 23 patients (63.9%) after 4hrs, 9 patients (25%) after 6hrs. compared to (control group 2) was mean=2.06hrs±SD0.72. where 8 patients (22.2%) had got free movement after 1hr, 18 (50%) after 2hrs and 10 (27.8%) after 3hrs.

Frequency Tables and Figures:

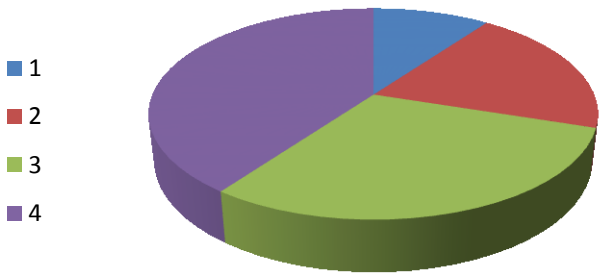
(Study group 1) Postoperative analgesia:

Hrs.	No.	%
4	5	13.9
5	13	36.1
6	14	38.9
7	4	11.1
Total	36	100



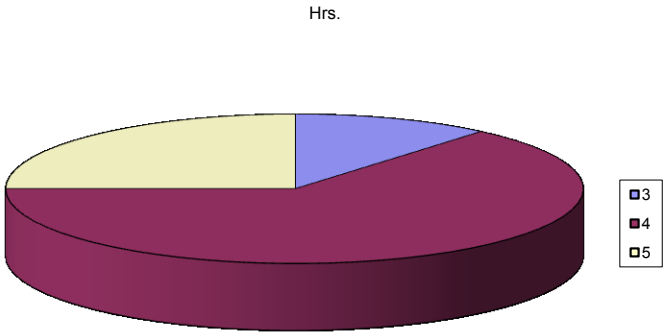
(Control group 2) Postoperative analgesia:

Hrs.	No.	%
1	1	2.8
2	16	44.4
3	17	47.2
4	2	5.6
Total	36	100



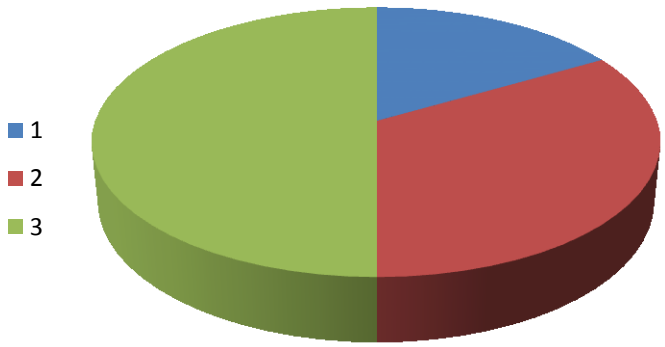
(Study group 1) postoperative motor block:

Hrs.	No.	%
3	4	11.1
4	23	63.9
5	9	25.0
Total	36	100



(Control group 2) postoperative motor block:

Hrs.	No.	%
1	8	22.2
2	18	50.0
3	10	27.8
Total	36	100



Discussion:

In this study, we found in (study group 1) that with the combination of heavy bupivacaine plus 50µg clonidine intrathecally for caesarean section patients provides very good sensory block up to T6 which abolishes any discomfortable sensation like skin traction or bowel manipulation that make patients complain during the surgery. In comparison to (control group 2) in which 40% patients complained.

The duration of postoperative analgesia in (study group 1) was prolonged, many patients has requested for analgesia after about 6hrs, compared with 2.5hrs for the control group.

The duration of postoperative motor block in (study group 1) was prolonged for about 4hrs,compared with 2hrs in (control group 2) ,this prolongation of motor block can be considered as side effect for intrathecally clonidine particularly when used epidural labour analgesia which may interferes with normal vaginal delivery especially with high doses more than 75 µg.

The hypotensive effect of clonidine was masked by the dense axonal blockade produced by heavy bupivacaine, the incidence of hypotension (drop in MAP >20%) was very close in both study groups for more than 50% of patients.

Decrease in HR up to less than 40b/min was only observed in two patients, one patient was affected due to high block and the other may be because of clonidine effect.

We did not observe any significant sedation effect with 50µg clonidine in any patients.

There was no effect on abgar score in neonates.

Conclusion:

From this study, we conclude that the addition of 50µg clonidine to the heavy bupivacaine intrathecally for caesarean section patients provides dense sensory block and improves the quality of intraoperative and postoperative sensory block, motor block and postoperative analgesia.

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