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Clinical Neuraxial Application of Clonidine- A Review

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ABSTRACT

Simple regional anaesthesia techniques like spinal,epidural,caudal anaesthesia have a definite useful role in developing countries like ours because of poor economic conditions and nonavailability of higher facilities. In this respect addition of various adjuvents like opiods and non opiods like clonidine to these neuraxial blockade techniques definitely provides prolonged analgesia,better musle relaxation,better suppression of various autonomic reflexes with minimum costs. The aim of my present study is to review the researches done with the use of clonidine,an α2 agonist in various neuraxial blocks along with local anaesthetic agents. Addition of clonidine in both spinal and epidural anaesthesia prolongs analgesia , motor blockade and suppresses the catecholamine release, resulting in better autonomic stability and patient outcome with minimum side effects.

KEYWORDS REGIONAL ANAESTHESIA,OPIODS, CLONIDINE,SPINAL ANAESTHESIA,EPIDURAL ANAESTHESIA

INTRODUCTION

Because of economic reasons as well as nonavailability of sophisticated anaesthetic equipments and medical gases for general anaesthesia, especially in rural and semiurban areas where a majority of our population resides, simple regional anaesthesia techniques like subarachnoid

block has got a definite and useful role in developing countries.

Spinal anaesthesia was initially produced inadvertently by Corning in 1885 and first used deliberately by Bier[1] in 1898. Glucose containing solution for spinal anesthesia was introduced by Barker[2] in 1907. Since then use of hyperbaric ("heavy") solution has been the tradition for spinal anaesthesia with lidocaine, bupivacaine, tetracaine and mepivacaine.

The first application of neuraxial opioids can be traced to that in 1901, when a Japanese surgeon used 10 mg intrathecal (IT) morphine with the local anaesthetic eucaine in two cancer patients .In 1979, Wang et al[3] observed significant analgesia with 0.5-1 mg spinal morphine. The use of IT hydrophilic opioids (usually morphine) quickly spread to perioperative care with excellent postoperative analgesia in a wide array of surgical procedures.

Though intrathecal or epidural opioids were among the first drugs (morphine was the first opioid administered intrathecally) used to augment neuraxial blocks other opioids used areFentanyl (commonest), Sufentanil, Alfentanil, Pethidine, Hydromorphone, Diacetylmorphine, Buprenorphine, Butorphanol various other non-opioid drugs have recently been proved to demonstrate analgesic effects.

Non-opioids :

a) alpha$_2$-adrenergic agonists: Clonidine, ST914 Tizanidine5 (experimental in rats)
b) Anticholinesterases: Neostigmine
c) Benzodiazepines: Midazolam
d) Steroids : Methylprednisolone
e) Ketamine

f) Endogenous nucleosides: Adenosine6 (experimental in rats)
g) Miscellaneous : Tenoxicam, Somatostatin, Octreotide, Droperidol, Calcitonin

CLONIDINE.

Clonidine is a selective partial agonist of α_2 adreno receptors. It is known to increase both sensory and motor block of local anaesthetics. The analgesic effect following its intrathecal administration is mediated spinally through activation of post synaptic α2 receptors in substantia gelatinosa of spinal cord.

The rationale behind intrathecal administration of clonidine is to achieve high drug concentration in the viscinity of α2 adrenoceptors in the Spinal cord and it works by blocking the conduction of C & Aδ fibres, increases potassium conductance in isolated neurons in vitro and intensifies conduction block of local anaesthetics. It can provide pain relief by an opiod independent mechanisms.

CLINICAL-NEURAXIAL APPLICATION OF CLONIDINE

Rockmann et al compared the analgesic effects of epidural clonidine (8 mcgkg-1) alone, with a lower dose (4 mcgkg-1) in combination with morphine (2 mg) or morphine (50mcgkg-1) alone in patients undergoing pancreatectomy.4 Epidural clonidine group had earlier onset of a longer duration of analgesia than when morphine alone was used. Haemodynamically, the clonidine treated patients had a rate dependent decrease in cardiac output.

It has also been observed that addition of clonidine (1mcgkg-1) to a caudal epidural solution of bupivacaine, improved the duration of postoperative analgesia without compromising ventilation.

Thirty-six geriatric patients, undergoing knee replacement using continuous spinal anaesthesia, were randomly assigned to receive bupivacaine alone or combined with either clonidine or morphine and the duration of surgical anaesthesia was assessed.5 Only 1/9 patients in the clonidine group received re-injection of bupivacaine for surgical pain compared with 8/11 patients in the morphine and 8/10 patients in the bupivacaine alone groups.

In another study, patients undergoing cesarean section were randomized to receive spinal anaesthesia with bupivacaine alone or supplemented with either clonidine or clonidine plus fentanyl intrathecally.6 The addition of clonidine improved the spread of sensory block and prolonged postoperative analgesia, but moderately increased sedation.

Lena et al[7] have shown that following IT morphine (4mcgkg-1) along with IT clonidine (1mcgkg-1) in a group of patients undergoing coronary artery bypass grafting (CABG) (IT injection performed before induction of G.A.), time to extubation was significantly lower, VAS scores were significantly lower and morphine dosage was significantly lower as compared with control group.

Research on ST-91, a polar analogue of clonidine

Recent experimental work by Duflo et al, with 2-(2,6-diethylphenylamine 2-imidazoline) (ST-91), a polar analogue of clonidine (acts on a 2-non A adrenoceptors) in rats have shown that intrathecal ST-91, seems to be an attractive alternative to clonidine as it produces analgesia in normal rats and in rats after nerve injury without significant hypotension, bradycardia, and sedation which are significant with clonidine. But human trials must await proper preclinical chemistry and toxicity studies. by others.[9,10]

Jean P. Racle et al[11]. (1987) had studied the prolongation of isobaric bupivacaine with epinephrine and clonidine in spinal anaesthesia. They concluded that clonidine 150 µg given intrathecally prolonged plain bupivacaine 0.5% spinal anaesthesia in elderly patients undergoing hip surgery and this technique was superior to the addition of adrenaline 200 µg to bupivacaine.

Torsen Gordh et al.[12] (1986) had evaluated the toxicity of subarachnoid clonidine. They found that when clonidine was administered in intrathecal space of rat in the dose of 1.63 µg or 16.3 µg for 14 consecutive days gave rise to no detectable neurotoxic changes in the doses employed.

F. Bonnet et. Al[13] In 1989 observed dose related prolongation of hyperbaric tetracaine spinal anaesthesia by clonidine in humans. They recorded 25% prolongation of sensory block at L_2 with 75 µg clonidine and 72% prolongation

Eisenach JC et al.[14] in 1989 demonstrated that extradural clonidine produces effective analgesia in a dose dependent fashion (100-300 µg) in patients with neuropathic pain and cancer pain.

O. Boico et al[15]. (1992) studied the effects of epinephrine and clonidine on plasma concentrations of spinal bupivacaine. They found that combining the epinephrine and clonidine with spinal bupivacaine lead to prolonged local anaesthetic blockade.

Van Essen et al[16] in 1992 reported that extradural clonidine 150 µg produced postoperative analgesia in patients undergoing abdominal hysterectomy.

Striebel HW[17] and co-worker in 1993 reported that in addition to antihypertensive and sympatholytic effect, clonidine had a sedative and analgesic action and decrease anaesthetic requirement during intraoperative period.

Fogarty DJ et al.[18] in 1993 compared the analgesic effects of intrathecal clonidine and intrathecal morphine after spinal anaesthesia in patients undergoing total hip replacement. They observed that both intrathecal clonidine and morphine prolonged the time to first analgesic compared to saline(clonidine mean 278mins,morphine 489mins saline 54 mins respectively)

Niemi L[19]. In 1994 studied the effects of intrathecal clonidine(3mcg/kg) on duration of bupivacaine spinal anaesthesia, haemodynamics and post operative analgesia in patients undergoing knee arthroscopy. He concluded that addition of clonidine prolongs sensory and motor anaesthesia of hyperbaric bupivacaine spinal anaesthesia, but marked haemodynamic changes and sedation may limit the usefulness of intrathecal clonidine.

W.Klimscha et al[20] studied the haemodynamics and analgesic effects of clonidine added repeatedly to continuous epidural and spinal blocks in a prospective,randomised,double-blind study of 40 patients scheduled for extremity orthopaedic surgery. They concluded that clonidine in spinal and epidural blocks prolong anaesthesia but can cause hypotention and bradycardia.

M. Gentil and F. Bonnet[13] in 1996 compared the incidence of urinary retention and rate of catheterization of bladder after intrathecal clonidine and intrathecal morphine. They concluded that the incidence of bladder dysfunction and catheterization was significantly less with intrathecally clonidine than morphine when used with spinal bupivacaine

De Negri P. Et al[21]. in 1997 found that the addition of clonidine to hyperbaric bupivacaine seems to be particularly useful in unilateral spinal anaesthesia, exerting minimal influence on haemodynamic parameters and guaranting a satisfactory postoperative analgesia.

Prof. Dr. Astrid Chiari,[22] University of Vienna in 1999 studied the effects of intrathecal clonidine and neostigmine on the duration and quality of anaesthesia produced by hyperbaric bupivacaine. He observed that addition of 150 µg clonidine to spinal or epidural bupivacaine improves the quality and increases the duration of postoperative and obstetric analgesia. However, administered intrathecally by itself, clonidine alone failed to produce reliable surgical anaesthesia despite a high dose of 450 µg.

I. Dobrydnjov and J. Samarutel[23] (1999) observed the enhancement of effect of intrathecal lidocaine by addition of local and systemic clonidine. They concluded that the addition of clonidine, 100 µg intrathecally or 300 µg orally, to lidocaine spinal anaesthesia prolongs the duration of sensory and motor blocks and permits a reduced lidocaine dose needed to a given duration of block.

Kaabachi O. Et al[24]have done a comparative study of hyperbaric bupivacaine with or without clonidine in spinal anaesthesia in children aged 6-15 years. They concluded that intrathecal clonidine 2 µg /kg is associated with extending duration of postoperative analgesia but with moderate side effects.

Dobrydnjov 1 et al[25] in 2002 studied the postoperative pain relief following intrathecal bupivacaine combined with intrathecal or oral clonidine. They concluded that the addition of intrathecal clonidine prolonged analgesia and decreased morphine consumption postoperatively more than oral clonidine. Intrathecal clonidine is therefore recommended.

Peggy perk et al,[26]found that intrathecal clonidine is effective for treatment of intractable non malignant pain.

Dobrydnjov I. Et al[23] in 2003 found that the addition of small dose of (15µg) clonidine of hyperbaric bupivacaine increases the spread of analgesia, prolongs the time to first analgesic request and decrease postoperative pain, compared with bupivacaine alone, during inguinal herniorrhaphy under spinal anaesthesia. Alain Borgeat[27] in Glasgow Meeting in May 2003 presented that there was no evidence that the risk of PONV (post operative nausea and vomiting) increases after addition of clonidine to various local anaesthetics.

A study by Brian D Sites et al[28] in 2003 showed that clonidine added to bupivacaine morphine anaesthesia improves postoperative analgesia in total knee arthroplasty.

Yoo-jing kang, James c Eisennachet al [29] showed in a study in 2003 that intrathecal clonidine reduces hypersensitivity after nerve injury by a mechanism involving spinal M4 muscarinic receptors.

Laurie –L Ackerman[30] in july 2003,studied the effectiveness of intrathecal clonidine or clonidine opiod combination for treatment of chronic pain states.

In jan 2004 Shin et al [31]carried out a study to evaluate the effect of spinal anaesthesia and intrathecal clonidine(75mcg) to reduce requirement of propofol for concious sedation.

Dobrydnjov I. Et al[32] in 2004 evaluated the effect of intrathecal and oral clonidine as supplements to spinal anaesthesia with lidocaine in patients at risk of postoperative alcohol withdrawal syndrome (AWS) and implement that clonidine 150 mcg both intrathecal and orally prevented postoperative AWS in alcohol dependent men.

In 2004, Strebel S. Et al.[33] examined a dose response relationship of intrathecal clonidine at small doses (37.5 µg, 75 µg and 150 µg) with respect to prolonging bupivacaine spinal anaesthesia for orthopaedic surgery. They concluded that although other small doses of intrathecal clonidine (37.5 µg and 75 µg) prolongs the analgesic and anaesthetic effects of spinal bupivacaine, 150 µg of clonidine seems to be the preferred dose, in terms of effect versus unwarranted side effects, when prolongation of spinal anaesthesia is desired.

In 2005, Y.T. Jeon et al.[34] compared the effectiveness of intrathecal and intravenous clonidine in suppressing post spinal shivering. They found that the intrathecal clonidine 150 µg fails to prevent post spinal shivering by contrast they have confirmed that i.v. Clonidine 1 µg/kg is an effective method to prevent shivering in patients undergoing spinal anaesthesia for orthopaedic surgery.

Alain Rochette et al.[35]in 2005 added clonidine to bupivacaine in neonatal spinal anaesthesia for herniorrhaphy in infants. They concluded that addition of clonidine to neonatal SA results in acceptable side effect of short apneas recovering spontaneously without desaturation.

Van Tujie al.[36] in 2006 evaluated the effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after caesarean section and demonstrated hat addition of 75 ug clonidine prolongs postoperative analgesia and moor block without clinically relevant maternal or neonatal side effects.

Patrica M. Lavand home et al [37]presented at ASA Annual meeting(oct 14-8-2006) an evaluation of postoperative antihypergesic and analgesic effects of intrathecal clonidine administered during elective caesarean section .They concluded that intrathecal clonidine 150 mcg caused significant reduction in the extent and incidence of periincisional punctuate mechanical hyperalgesia at 48 hrs compared to bupivacaine alone.

Belhadi Amor M[38]. And group in2007 reported that intrathecal clonidine (30 mcg) prolong labor analgesia but increase incidence of hypotension and abnormal foetal heart rate.

In 2007 B.S. Sethi[39] and colleagues studied the efficacy of analgesic effects of low dose intrathecal clonidine (1 ug/kg) with bupivacaine concluded that addition of clonidine significantly increases the duration of spinal analgesia as compared to bupivacaine alone with clinically insignificant influence on hemodynamic parameters and level of sedation, an as effective as higher dosage minimizing the side effects.

Grandhe RP et al.[40] in 2007 stated that addition of intrathecal clonidine (1 ug/kg) with bupivacaine for unilateral spinal block prolongs the duration of anaesthesia and postoperative analgesia.

Recently 2007 Levand Homme PM et al.[41] evaluated the postoperative antihyperalgesic and analgesic effects of intrathecal clonidine (150 mcg) with bupivacaine during elective caesarean delivery.

Grandhe RP carried out a study in 2008 to evaluate the perioperative analgesic effects of bupivacaine –clonidine combination for unilateral spinal anaesthesia in lower limb orthopaedic surgeries and concluded that addition of clonidine prolongs duration of anaesthesia and postoperative analgesia with minimal side effects

Recently R. Sunder[42] in 2009 studied the different dose of intrathecal clonidine (30, 45, 75, 105 and 150 mcg) for major lower limb arthroplasty and evaluated that optimal dose for better quality of anaesthesia and analgesia with low dose hyperbaric bupivacaine is 75 mcg.

E- I uhle ,R Becker et al[43]studied continuous intrathecal clonidine administered for treatment of neuropathic pain(44mcg/ day)and concluded that 70-100% reduction in pain was achieved.

CONCLUSION

Thus from these various studies,we can conclude that addition of inj.Clonidine to local anaesthetic agents in spinal and epidural anaesthesia significantly prolongs analgesia , motor blockade and suppresses sympathetic surges and thus maintains a stable haemodynamics with minimum side effects

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