Effectiveness of bupivacaine and tramadol in postoperative pain management - A prospective study

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Abstract

Background: Surgeries are associated with significant postoperative pain. Postoperative pain is usually of longer duration and recurs after few hours. The caudal epidural block is considered as the procedure of choice for pain relief in such cases. The purpose of this study is to evaluate the postoperative analgesic efficacy of epidurally administered Bupivacaine and Tramadol in surgeries including cesarean sections and other gynecological surgeries.

Aim of the Study: Effectiveness of bupivacaine and tramadol in postoperative pain management

Materials and methods: A total of 100 cases were included in this study between the age group of 15 years and 65 years. They were grouped into group A - Bupivacaine group and group B - Tramadol group.

Results: The mean interval between 1st and 2nd dose in Group A was 268.15 minutes and in Group B was 398.35 minutes. Dose intervals between 2nd and 3rd dose in Group A were 279.52 minutes and in Group B 371.41 minutes. Dose intervals between 3rd and 4th dose in Group A were 266.42 and in Group B was 321.15 minutes. There were no cases which required the 4th dose of the drug in this study.

Conclusion: Postoperative consumption of analgesia was higher in the Bupivacaine group. Epidural tramadol 100 mg in 10 ml provides better and longer duration of anesthesia with rapid onset and no incidence of complications.
Introduction

As the complexity of the surgical procedures continues to grow, anesthetists are being challenged to provide patients with optimal surgical experience, good operating conditions and rapid recovery time without many side effects. Pain itself is the highly unpleasant sensory and emotional experience [1]. Regardless of the anesthesia technique, prevention and treatment of the postoperative pain must be addressed and same modalities should be available for all types of anesthesia. Inguinal hernia repair and appendicectomies and gynecological surgeries are usually associated with persistent postoperative discomfort and distress for the patient which results in an extended hospital stay. Several clinical methods and techniques have been implemented to extend the duration of regional anesthesia with local anesthetics. Caudal epidural block remains a popular and conventional anesthetic tool for control of such pain. Bupivacaine is the currently available local anesthetics with long duration of action and its maximum analgesic effect is up to 6-12 hours [2, 3]. Many drugs including epinephrine, opioids, clonidine, ketamine, midazolam, and neostigmine have been tried as adjuvants with caudal bupivacaine to improve the quality of analgesia and extend its duration but each of these has its own documented adverse effects [4]. The primary aim of this study was to compare the pharmacological analgesic efficacy of four different doses of tramadol 100mg versus bupivacaine 0.25% used separately in postoperative pain management of forty adult cases of gynecological surgery and identify which drug at which dose had a maximum duration of epidural analgesia.

Aim of the study

Effectiveness of bupivacaine and tramadol in postoperative pain management.

Materials and methods

This study was carried out at Mahavir Institute of Medical Sciences, Vikarabad, Telangana State. A total of 100 cases were included in the study. Informed written consent was taken from the patients and ethical clearance was obtained from the Institutional ethics committee. Age group included in this study was 15 years to 65 years. All elective surgery cases requiring epidural anesthesia were included in this study. These cases were grouped as Group A (50 cases) and Group B (50 cases). Group A received Bupivacaine 0.25% and Group B received Tramadol 100mg. Cases, where there was a contraindication to the use of the above drugs, cases with history of cardio-respiratory illness, cases with drug sensitivity for the above drugs, cases with neurological, spinal and sacral degenerations and cases with increased intracranial tension, were excluded from the study.

All cases were examined one day before the study. The epidural technique was clearly explained to them in their regional language. They were also informed that in case of failure of epidural anesthesia they would be induced with general anesthesia, in that case, they would automatically get excluded from this study. All cases were directed to remain nil by mouth from the morning of the study. They were given premedication 5mg Diazepam orally on the night before surgery. All cases were preloaded with 1000ml of Ringer’s Lactate through a 16G intravenous cannula before proceeding for the operation theatre. For administration of epidural anesthesia, 18G Tuohy needle an epidural catheter was prepared. In conventional position, for spinal anesthesia, the L3-L4 intervertebral space was marked and a small wheal was made by subcutaneous infiltration of 2 ml of 2% lignocaine. A small nick was then made over the wheal and the 18G Tuohy needle was introduced until the ligamentum flavum was pierced. The
stylette was withdrawn and a 5 ml glass syringe with smoothly moving piston was attached tightly to the hub of the Tuohy needle. The needle was slowly moved until there was the loss of resistance. This indicated the epidural space. The catheter was then threaded to the epidural space and the needle was removed. The catheter was then fixed with a transparent occlusive dressing and 15ml of 2% Xylocaine was injected through the catheter. This produced desirable anesthesia for the surgeon to perform surgery. 

Post surgery the cases were transferred to the postoperative ward for pain management and resuscitation. The cases were now randomly allocated to one of the study groups. The drugs under this study were randomly injected when the analgesic effect was demanded by the subject. This was the first dose and the time was recorded. Each case was visited at 2nd, 4th, 8th, 12th and 24 hours after the first dose. At each visit, the VAS score was recorded along with pulse rate, blood pressure, and breathing rate. The drug was repeated on demand by the cases and time of each additional dose was recorded. A maximum of four doses of each drug was permissible under this study and cases with severe persistent pain were given a rescue dose of 75 mg intravenous Pethidine and excluded from the study being considered a failure case. The time of administration of rescue dose was also noted. After 24 hours, the epidural catheter was removed and pain management was left at the discretion of the attending specialist.

**Results**

A total of 100 cases were included in the study. Age group included in this study was 15 years to 65 years. Male patients were 41 and female patients were 59. The mean age in the study being 38.65 years for Group A and 39.35 years for Group B.

In this study, the surgical cases picked randomly were Total abdominal hysterectomy, vaginal hysterectomy, hysterectomy with tubectomy, surgeries on cervix, pelvic floor repair, fistulas and fissures, and other explorative laparotomies (Table - 1). They were divided group wise into Group A and Group B.

**Table - 1: The types of surgeries performed.**

<table>
<thead>
<tr>
<th>Surgery performed</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total abdominal hysterectomy</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Vaginal hysterectomy</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hysterectomy with tubectomy</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Repair of cervix and pelvic floor</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fistula and fissures</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Appendicectomy</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Herniorrhaphy</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Other laparotomies</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

The mean interval between 1st and 2nd dose in Group A was 268.15 minutes and in Group B was 398.35 minutes. Dose intervals between 2nd and 3rd dose in Group A was 279.52 minutes and in Group B 371.41 minutes. Dose intervals between 3rd and 4th dose in Group A was 266.42 and in Group B was 321.15 minutes. There were no cases which required 4th dose of drug in this study.

In this study, some of the patients experienced some side effects of the drugs used. Some of the side effects experienced were nausea and vomiting, numbness in lower limbs, shivering, respiratory depression, pruritus, dizziness and inability to walk after 24 hour period (Table - 2).

**Table – 2: Side effects.**

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Group A (n=50)</th>
<th>Group B (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>Numbness in the lower limbs</td>
<td>12</td>
<td>NIL</td>
</tr>
<tr>
<td>Shivering</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Inability to walk after 24 hours</td>
<td>9</td>
<td>4</td>
</tr>
</tbody>
</table>
Discussion

Bupivacaine was discovered in 1957 [5]. It is on the World Health Organization’s (WHO) list of Essential Medicines. Bupivacaine is the most effective and safe medicines in a health system [6]. Bupivacaine is a medication used to decrease feeling in a specific area [7]. It is used by injecting it into the area, around a nerve that supplies the area, or into the spinal canal's epidural space. It is available mixed with a small amount of epinephrine to make it last longer [7]. It typically begins working within 15 minutes and lasts for 2 to 8 hours [7, 8]. Bupivacaine is indicated for local infiltration, peripheral nerve block, sympathetic nerve block, and epidural and caudal blocks. It is sometimes used in combination with epinephrine to prevent systemic absorption and extend the duration of action. The 0.75% (most concentrated) formulation is used in retrobulbar block [9]. It is the most commonly used local anesthetic in epidural anesthesia during labor, as well as in postoperative pain management [10]. Bupivacaine is contraindicated in patients with known hypersensitivity reactions to bupivacaine or amino-amide anesthetics. It is also contraindicated in obstetrical paracervical blocks and intravenous regional anesthesia (Bier block) because of potential risk of tourniquet failure and systemic absorption of the drug and subsequent cardiac arrest. The 0.75% formulation is contraindicated in epidural anesthesia during labor because of the association with refractory cardiac arrest [11]. Possible side effects include sleepiness, muscle twitching, ringing in the ears, changes in vision, low blood pressure, and an irregular heart rate. Concerns exist that injecting it into a joint can cause problems with the cartilage. Concentrated bupivacaine is not recommended for epidural freezing. Epidural freezing may also increase the length of labor. It is a local anesthetic of the amide group. Bupivacaine binds to the intracellular portion of voltage-gated sodium channels and blocks sodium influx into nerve cells, which prevents depolarization. Without depolarization, no initiation or conduction of a pain signal can occur.

Tramadol was launched and marketed as "Tramal" by the German pharmaceutical company Grünenthal GmbH in 1977 in West Germany, and 20 years later it was launched in countries such as the UK, US, and Australia [12]. It is marketed under many brand names worldwide [13]. Tramadol is an opioid pain medication used to treat moderate to moderately severe pain [13]. When taken as an immediate-release oral formulation, the onset of pain relief usually occurs within about an hour [14]. It has two different mechanisms. First, it works by binding to the μ-opioid receptor [15]. Second, it inhibits the reuptake of serotonin and norepinephrine [12, 16]. It is often combined with paracetamol (acetaminophen) as this is known to improve the efficacy of tramadol in relieving pain [17]. Serious side effects may include seizures, increased risk of serotonin syndrome, decreased alertness, and drug addiction, although the risk of serotonin syndrome appears to be low. Common side effects include constipation, itchiness and nausea, among others. A change in dosage may be recommended in those with kidney or liver problems. It is not recommended in those who are at risk of suicide. While not recommended in women who are breastfeeding, those who take it should not stop breastfeeding [18]. tramadol mainly acts as a μ-opioid receptor agonist [15, 19], serotonin reuptake inhibitor and releasing agent, norepinephrine reuptake inhibitor [19], NMDA receptor antagonist (IC50= 16.5 μM) [20], 5-HT2C receptor antagonist (EC50 = 26 nM), (α7)5 nicotinic acetylcholine receptor antagonist,TRPV1 receptor agonist, and M1 and M3 muscarinic acetylcholine receptor antagonist [21, 22]. Some of the additional affinity of tramadol have been reported as follows: μ-opioid receptor (Ki = 2.1 μM), κ-opioid receptor (Ki = 42.7 μM), δ-opioid receptor (Ki = 57.6 μM), serotonin transporter (Ki = 0.99 μM), norepinephrine transporter (Ki = 0.79 μM). Relative to tramadol, its active metabolite O-desmethyltramadol has far higher affinity for the
μ-opioid receptor (Ki = 3.4 nM (0.0034 μM) for the (+)-isomer). Its analgesic effects are only partially reversed by naloxone, hence indicating that its opioid action is unlikely the sole factor; tramadol’s analgesic effects are also partially reversed by α2 adrenergic receptor antagonists like yohimbine and the 5 HT3 receptor antagonist, ondansetron [23]. Pharmacologically, tramadol is similar to levorphanol and tapentadol in that it not only binds to the mu opioid receptor but also inhibits the reuptake of serotonin and norepinephrine due to its action on the noradrenergic and serotonergic systems, such as its "atypical" opioid activity.

Tramadol has inhibitory actions on the 5-HT2C receptor. Antagonism of 5-HT2C could be partially responsible for tramadol’s reducing effect on depressive and obsessive-compulsive symptoms in patients with pain and comorbid neurological illnesses [24]. 5-HT2C blockade may also account for its lowering of the seizure threshold, as 5-HT2C knockout mice display significantly increased vulnerability to epileptic seizures, sometimes resulting in spontaneous death. However, the reduction of seizure threshold could be attributed to tramadol’s putative inhibition of GABAA receptors at high doses. In addition, tramadol’s major active metabolite, O-desmethyl tramadol, is a high-affinity ligand of the δ- and κ-opioid receptors, and activity at the former receptor could be involved in tramadol’s ability to provoke seizures in some individuals, as δ-opioid receptor agonists are well known to induce seizures.

In our present study, we found lower VAS pain scores and a longer duration of postoperative analgesia and a much significant decrease in the 24 h consumption of rescue anaesthesia in Group B. There was also earlier recovery of unassisted ambulation and home discharge [24]. No significant side effects were detected in any group. Although tramadol was initially considered to be a weak μ-opioid agonist, it appears to have multimodal mechanisms of action. It is now accepted that in addition to μ-opioid agonist effect, tramadol enhances the function of the spinal descending inhibitory pathway by inhibition of reuptake of both 5-hydroxytryptamine (5-HT) and norepinephrine, together with pre-synaptic stimulation of H-HT release [25, 26].

The local anesthetic action of tramadol remains unproven. 5-HT3 receptors are exposed on the peripheral and spinal terminals of the nociceptive primary afferent fibers as well as on the superficial lamina of the dorsal horn which indicates possible peripheral sites of action of tramadol [27, 28]. Studies have shown a definitive local anesthetic effect of tramadol in experiments on frog sciatic nerves revealing that the nerve conduction block of tramadol is 3-6 times weaker than that of lidocaine. Although lidocaine inhibits Na+ channels, it is suggested that tramadol inhibits K+ channels. A headache, nausea, vomiting, dizziness, somnolence are major side effects of IV tramadol when used for postoperative analgesia [29]. Such incidence seems to be directly related to peak serum concentration levels of tramadol. Activation of hypothalamic-pituitary-adrenal axis and the rise of cortisol and epinephrine plasma levels associated with surgical trauma are very important postoperative stress responses. Caudal tramadol has more analgesic efficacy than bupivacaine [30]. In equipotent analgesic doses of tramadol to morphine is free of respiratory symptoms [31].

**Conclusion**

The present study concluded that both epidurally administered bupivacaine and tramadol are potent, safe and effective postoperative analgesics. Postoperative consumption of analgesic was higher in the Bupivacaine group. Epidural tramadol 100 mg in 10 ml provides better and longer duration of anesthesia with rapid onset and no incidence of complications.

**References**

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23. Ogata J, Minami K, Uezono Y, Okamoto T, Shiraishi M, Shigematsu A, Ueta Y. The inhibitory effects of tramadol on 5-hydroxytryptamine type 2C receptors expressed in Xenopus


