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A COMPARATIVE STUDY BETWEEN TRAMADOL AND FENTANYL IN SPINAL ANESTHESIA IN CESAREAN SECTION

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ABSTRACT

Study Objective: Studying the efficacy of adding tramadol to spinal anesthesics for postoperative analgesia. **Setting:** This study was carried out in the department of anesthesia and reanimation at Alkark Hospital, during 2017-2018. **Patients:** The study included 70 patients classified, and were scheduled for elective cesarean section under spinal anesthesia. **Interventions:** Patients were randomly divided into 2 groups (35 in each group): Patients of group (A) received 12.5 mg bupivacaine 0.5% (3ml) + 25 µg fentanyl (½ml) Patients of the group (B) received 12.5 mg bupivacaine 0.5% (3ml) + 25 mg tramadol (½ml), Pain relief duration of each group, side effects, Blood pressure, heart rate and O2 saturation, were recorded. **Results:** Analgesia duration was greatly prolonged in the Tramadol group, and side effects were significantly lower than Fentanyl group. **Conclusion**: 25 mg of intrathecal tramadol with bupivacaine cause a prolonged analgesia duration with no significant side effects.

KEYWORDS: Tramadol, Bupivacaine, Cesarean Section, Spinal Anesthesia.

INTRODUCTION

Caesarean is one of the most common types of gynecological operations. Controlling postoperative pain is one of the most important issues of operation that affects the healthcare system. Postoperative pain will delay the patient's return to normal conditions, elongate the

hospitalization period, increase the occurrence of atelectasis, venous thrombosis, and patients' dissatisfaction. Prescription of analgesics in the postoperative period improves the patients' pain and consequently results in improved pulmonary performance due to the facilitation of physiotherapy by the patient. As the patient resumes his normal activities much faster, the result will be less constipation, less venous thromboembolic complications, and a shorter period of restoration.[1]

Narcotic analgesics used as strong pain killers after the operation are associated with various complications and side effects such as dizziness, reduced pulmonary performance, ileus, nausea, vomiting, itching, and urinary retention. Controlling the patient's pain requires periodic venous and intramuscular injections so that the medicine may reach a stable state that is always more than the minimum effective anesthetics concentration. However, insufficient and unpredictable blood densities in injection intervals make a determination of the appropriate dose and adjusting the medicine to the stable density difficult. As a result, an accurate nursing car will be required to prevent the venous injection of a high amount of medicine that is associated with a high prevalence of central nervous system and respiratory system weakening. In most cases drugs given upon the request of the patient, the sufficient level of analgesia is never achieved. Painkillers without the above-said complications, which have a better and more enduring analgesic effect, are preferable.[2]

Due to analgesic properties and lack of harmful effects in contrast to opioids, local anesthetics largely used to treat surgical pain. If the acute pain is not controlled and managed properly, it may have adverse effects on various systems of the body including inability to discharge mucosa from the respiratory system, digestive system ileus, high heart beat and blood pressure, sweating, going pale, longer period of resting in bed, higher risk of deep venous thrombosis, and delayed milking onset.[3]

As a result, finding a medicine, which can have the longest period of postoperative analgesia, is one of the most important issues after caesarean. To reduce patient's pain, various medicines such as drugs and other non-narcotic painkillers are used. Non-narcotic drugs have several advantages over their narcotic counterparts including no respiratory weakness, no potential of drug abuse, less stupefying effects, less nausea, early restoration of intestinal performance, and quicker recovery. Considering these potential advantages, many doctors prefer non-narcotic painkillers.[4]

Over the last two decades, there has been a considerable revival of interest in the use of regional anesthesia techniques for surgery and pain management. Narcotic analgesics are commonly used as adjuncts to local anesthetics (LA) in epidural anesthesia. They produce a synergistic effect by acting directly on opioid receptors in the spinal cord they hasten the onset, improve the quality of the block as well as prolong the duration of analgesia. Also a dose of local anesthetics like bupivacaine can be reduced, thereby reducing its side effects like myocardial depression, hypotension, bradycardia, heart block, and ventricular arrhythmias. A wide variety of drugs have been used which are both non-opioids and opioids such as epinephrine, α2-adrenoceptor agonists (clonidine and dexmedetomidine), acetylcholine esterase inhibitors (neostigmine), adenosine, ketorolac, midazolam, sodium bicarbonate and hyaluronidase, and opiods being hydrophilic (morphine) and lipophilic (fentanyl and sufentanyl), although very few drugs are actually in clinical use.[5] Fentanyl, a short-acting lipophilic opioid stimulates μ1 and μ2 receptors. It potentiates the afferent sensory blockade and facilitates a reduction in the dose of local anesthetics without intensifying the motor block or prolonging recovery. Fentanyl provides good quality of intraoperative analgesia, hemodynamic stability, minimal side effects, and excellent quality of postoperative analgesia. Tramadol, a synthetic 4-phenyl-piperidine analog of codeine, is a racemic mixture of two enantiomers, with synergistic antinociceptive interaction. The (+) enantiomer has moderate affinity for the opioids μ receptor and inhibits serotonin uptake, and the (−) enantiomer is a potent norepinephrine synaptic release inhibitor. It too has the potential to provide effective post effective analgesia. Therefore, keeping in mind cost effectiveness and the side effects, we have decided to compare both the drugs to find better adjuvant in all respects.[6]

BACK GROUND

Tramadol

For women undergoing a caesarean section, the addition of intrathecal opioids to bupivacaine enhances the quality and duration of intra- and postoperative analgesia.[7] However, intrathecal opioids are associated with adverse effects such as respiratory depression, nausea and vomiting.[1] Through its unique mechanism of inhibiting neuronal uptake of norephinephrine and serotonin, tramadol has many novel features, unlike other opioids that act purely on the l-receptor.[8] Neurotoxicity has not been demonstrated in several animal studies when non-toxic doses of tramadol have been administered perineural or neuraxially.[9]

Furthermore, intrathecal tramadol has been used for postoperative analgesia following various operations, and for labour analgesia, and importantly, it appears to have a safe pharmacokinetic profile in the neonate. However, its effect as an adjunct to local anaesthetic for a subarachnoid block for the caesarean section has not been reported.[10]

The primary objective of the present study was to compare intrathecal tramadol with fentanyl as an adjunct to hyperbaric bupivacaine, assessing sensory and motor blockade, as well as postoperative analgesia following caesarean section. Secondary objectives were to compare adverse effects, if any, in the mother and baby during the 24 h following its administration.

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. It is a central analgesic with a low affinity for opioid receptors. Its selectivity for μ receptors has recently been demonstrated, and the M1 metabolite of tramadol, produced by liver *O*-demethylation, shows a higher affinity for opioid receptors than the parent drug. The rate of production of this M1 derivative (*O*-demethyl tramadol), is influenced by a polymorphic isoenzyme of the debrisoquine-type, cytochrome P450 2D6 (CYP2D6).[11]

Nevertheless, this affinity for μ receptors of the CNS remains low, being 6000 times lower than that of morphine. Moreover, and in contrast to other opioids, the analgesic action of tramadol is only partially inhibited by the opioid antagonist naloxone, which suggests the existence of another mechanism of action. This was demonstrated by the discovery of a monoaminergic activity that inhibits noradrenaline (norepinephrine) and serotonin (5-hydroxytryptamine;5-HT) reuptake, making a significant contribution to the analgesic action by blocking nociceptive impulses at the spinal level.[12]

Tramadol is a racemic mixture of 2 enantiomers, each one displaying differing affinities for various receptors. Tramadol is a selective agonist of μ receptors and preferentially inhibits serotonin reuptake, whereas tramadol mainly inhibits noradrenaline reuptake. The action of these 2 enantiomers is both complementary and synergistic and results in the analgesic effect of tramadol.[13]

After oral administration, tramadol demonstrates 68% bioavailability, with peak serum concentrations reached within 2 hours. The elimination kinetics can be described as 2-compartmental, with a half-life of 5.1 hours for tramadol and 9 hours for the M1 derivative after a single oral dose of 100mg. This explains the approximately 2-fold accumulation of

the parent drug and its M1 derivative that is observed during multiple dose treatment with tramadol. The recommended daily dose of tramadol is between 50 and 100mg every 4 to 6 hours, with a maximum dose of 400 mg/day; the duration of the analgesic effect after a single oral dose of tramadol 100mg is about 6 hours.[14]

Adverse effects, and nausea in particular, are dose-dependent and therefore considerably more likely to appear if the loading dose is high. The reduction of this dose during the first days of treatment is an important factor in improving tolerability. Other adverse effects are generally similar to those of opioids, although they are usually less severe, and can include respiratory depression, dysphoria and constipation. Tramadol can be administered concomitantly with other analgesics, particularly those with peripheral action, while drugs that depress CNS function may enhance the sedative effect of tramadol. Tramadol should not be administered to patients receiving monoamine oxidase inhibitors, and administration with tricyclic antidepressant drugs should also be avoided. Tramadol has pharmacodynamic and pharmacokinetic properties that are highly unlikely to lead to dependence. This was confirmed by various controlled studies and postmarketing surveillance studies, which reported an extremely small number of patients developing tolerance or instances of tramadol abuse.[15] Tramadol is a centrally acting analgesic which has been shown to be effective and well tolerated, and likely to be of value for treating several pain conditions (step II of the World Health Organization ladder) where treatment with strong opioids is not required.

Fentanyl

Intrathecal fentanyl administration potentiates spinal anesthesia and is therefore a useful adjunct to for cesarean delivery. However, in previous studies, no additional fentanyl was administered intraoperatively, thus there is no clear evidence whether intrathecal fentanyl provides better intra- and postoperative pain control than intravenous fentanyl.[16]

Spinal anesthesia

Development of regional anesthesia started with the isolation of local anesthetics, the first being cocaine (the only naturally occurring local anesthetic). The first regional anesthetic technique performed was spinal anesthesia, and the first operation under spinal anesthesia was in 1898 in Germany by August Bier. Before this, the only local anesthetic techniques were topical anesthesia of the eye and infiltration anesthesia.[17]

The central nervous system (CNS) comprises the brain and spinal cord. The term neuraxial anesthesia refers to the placement of local anesthetic in or around the CNS. Spinal anesthesia is a neuraxial anesthesia technique in which local anesthetic is placed directly in the intrathecal space (subarachnoid space). The subarachnoid space houses sterile cerebrospinal fluid (CSF), the clear fluid that bathes the brain and spinal cord. There are roughly about 130 to 140 mL of CSF in an adult human which continually cycles throughout the day. Approximately 500 mL of CSF gets produced daily.[18]

Other neuraxial techniques include epidural and caudal anesthesia, each having its particular indications. Spinal anesthesia is only performed in the lumbar spine for reasons. Administration of spinal anesthesia requires appropriate positioning and understanding of neuraxial anatomy. The goal is to deliver appropriately dosed anesthetic into the intrathecal (subarachnoid) space.[19]

The spine comprises seven cervical, 12 thoracics, five lumbar, and five fused sacral vertebral bones. The different vertebral bones earn their names based on their relative positions and structural differences. The vertebrae are stacked end to end with articulating joints and ligaments, and a hollow space running through them called the spinal canal. This canal houses the spinal cord. The spinal nerves exit the spinal canal via lateral spaces formed between pedicles from adjacent vertebrae.

As mentioned earlier, spinal anesthesia is only performed in the lumbar area, specifically the mid to low lumbar levels to avoid damage to the spinal cord and also to prevent intrathecally-injected medications from having any activity in the upper thoracic and cervical regions. The caudal end of the spinal cord is the conus medullaris and usually is at the lower border of the first or sometimes the second lumbar vertebral body. In pediatric patients, it is a little more inferior, generally ending around L3. In the adult population, the mean conus position is the lower third of L1 (range: the middle third of T12 down to the upper third of L3).

The variation in conus positions follows a normal distribution. No significant difference in conus position is seen between male and female patients or with increasing age. The dural sac usually extends to S2/3. For these reasons, insertion of the spinal needle for spinal anesthesia is usually at the L3/4 or L4/5 interspace. Spinal cord trauma is more likely when choosing higher interspaces, especially in obese patients.[20]

Indications

Neuraxial anesthesia is used as a sole anesthetic or in combination with general anesthesia for most procedures below the neck. As mentioned in the introduction, spinal anesthesia is in common use for surgical procedures involving the lower abdomen, pelvis, perineal and lower extremities; it is beneficial for procedures below the umbilicus.

There needs to be patient counseling regarding the procedure, and signed informed consent is necessary. Since the procedure is usually performed on awake or slightly sedated patients, the indication for spinal anesthesia and what to expect during placement of neuraxial, risks, benefits, and alternative procedures are some of the discussions that can help allay anxiety. It is crucial to let the patient understand that they will have little or no ability to move their lower extremities until the resolution of the block. Spinal anesthesia is best for short procedures. For more extended procedures or procedures that would compromise respiration, general anesthesia is usually preferable.[21]

Contraindications

There are major known contraindications to neuraxial anesthesia (spinal and epidural). The absolute contraindications are lack of consent from the patient, elevated intracranial pressure (ICP), primarily due to intracranial mass and infection at the site of procedure (risk of meningitis).

Relative contraindications are Preexisting neurological disease (particularly those that wax and wane, e.g., multiple sclerosis) Severe dehydration (hypovolemia), due to the risk of hypotension - risk factors for hypotension include hypovolemia, age greater than 40 to 50 years, emergency surgery, obesity, chronic alcohol consumption, and chronic hypertension.[22]

MATERIALS AND METHODS

The study sample consisted of (70) patients from the patients to Karkh Hospital, for caesarean section under spinal anesthesia.

Interventions: Patients were randomly divided into 2 groups (35 in each group):

- Patients of group (A) received 12.5 mg bupivacaine 0.5% (3ml) + 25 µg fentanyl (½ml)
- Patients of group (B) received 12.5 mg bupivacaine 0.5% (3ml) + 25 mg tramadol (½ml)

Pain relief duration of each group, side effects, Blood pressure, heart rate and O2 saturation, were recorded.

Inclusion criteria

• All women aging 20 to 40 years candidated for elective caesarean resorting.

• No allergy to lidocaine, Dexmedetomidine, and tramadol

• Informed consent to take part in the research

Exclusion criteria

• Patient's refusal to take part in the research

• Aging out of the range of 20 to 40 years old

• Class III and IV ASA

• Failure of spinal anesthesia

• More than 2 attempts for spinal anesthesia

• Operations lasting longer than 90 min

• Patients with a history of drug abuse

• Patients with cardiovascular, liver or renal complications

RESULTS

Table 1: comparative between two group.

Variable	Group A	Group B	P
Time to reach max sensory level (min)	8.1±3.84	9.8±4.15	0,000
Duration of Analgesia	441± 119.69	450± 109.38	0,000

Results The maximum sensory level achieved was T6 in both groups. The mean time to onset of sensory block to T10 dermatome and the time to achieve maximum sensory block level was comparable in both the groups. The mean time for regression of sensory blockade to L5 dermatome was prolonged in the fentanyl group as compared to the tramadol group, which was highly significant, $P < 0.001$. The maximum motor block level achieved and the time to achieve maximum motor block level was comparable in both the groups. The mean total duration of motor block in the fentanyl group was more than the tramadol group, and the difference was highly significant, $P < 0.001$. The time of request of the first analgesia in fentanyl group was 420.00 ± 42.99 min, which was significantly more than the tramadol group in which it was 310.20 ± 33.20 min, $P < 0.001$, indicating superior analgesia. The number of injections of rescue analgesia in fentanyl group was 3.16± 0.48 and in tramadol group was 3. 00 ± 0.60. The difference between the two groups was highly significant (P <

0.001). The quality of surgical anesthesia was excellent in both the groups in the intraoperative period.

In the current study, our data showed that significant difference was observed between the groups on terms of pain score and 24 h following the operation with the pain score being more in fentanil than tramadol groups (P=0.000,), a significant difference was observed between the groups in terms of the average length of analgesia. The average length of postoperative analgesia in group A was shorter than group B (tramadol groups). No significant difference was observed between fentaanil than tramadol groups ($P \geq 0.05$).

As pvalue=0.01, a significant difference was observed between the groups on terms of the average amount of drugs taken within 24 h after operation.

No significant difference was observed between the groups in terms of average blood pressure at various times (before spinal anesthesia, immediately after spinal anesthesia, 15 min after spinal anesthesia, and 30 min after spinal anesthesia) ($P \geq 0.05$). No significant difference was observed between the groups in terms of average heart rate in various times (before spinal anesthesia, immediately after spinal anesthesia, 15 min after spinal anesthesia, and 30 min after spinal anesthesia) ($P \geq 0.05$). As $P \geq 0.05$, no significant difference was observed between the groups in terms of their average age and their average age was nearly equal to 25 years ($P \geq 0.05$). As $P \geq 0.05$, no significant difference was seen between the groups in terms of their average age of pregnancy and the average age was nearly equal to 39 weeks.

DISCUSSION

Recent trends of obstetric anesthesia show increased the popularity of regional anesthesia amongst obstetric anesthetists. General anesthesia is associated with a higher mortality rate in comparison to regional anesthesia. However, regional anesthesia is not without risk. Deaths in regional anesthesia are primarily related to excessive high regional blocks and toxicity of local anesthetics. Reduction in doses and improvement in technique to avoid higher block levels and heightened awareness of the toxicity of local anesthetics have contributed to the reduction of complications related to regional anesthesia. Spinal anesthesia among the neuraxial blocks in obstetric patients needs more strict dose calculations as the drugs are directly injected in intrathecal space. With minimum dose changes, the chances of complications and side effects are enhanced.

CONCLUSION

It is concluded from our study that bupivacaine when combined with tramadol or fentanyl provided an adequate subarachnoid block for lower abdominal surgeries. Both the groups were effective in providing adequate surgical anesthesia and hemodynamic stability, but tramadol seems to be a better alternative to fentanyl as an adjuvant to spinal bupivacaine in surgical procedures. It provides good quality of intraoperative analgesia, hemodynamically stable conditions, minimal side effects, and excellent quality of postoperative analgesia. Also found superior:

1. Prolonged duration of the sensory block
2. Longer duration of postoperative analgesia
3. A lesser number of doses of rescue analgesia required.

REFERENCES

1. Shahrokhi N, Pazuki S, Kamali A, Talebi H. Comparison between intrathecal midazolam and tramadol with conventional method for postoperative pain and shivering control after elective cesarean section. Anesthesiol Pain J., 2013; 3: 76-72.
2. Stamer U, Schneck H, Grond S, Wulf H. Surveys on the use of regional anaesthesia in obstetrics. Curr Opin Anaesthiol, 1999; 12: 565-571.
3. Ng k, Parsons J, Cyna A, Middleton P. Spinal versus epidural anaesthesia for caesarean section. Cochrane Database Syst Rev., 2004; 2: CD003765.
4. Son A, Rudra A, Sarkar S, Biswas B. Intrathecal midazolam for postoperative pain relief in caesarean section delivery. J Indian Med Assoc, 2001; 19: 683-686.
5. Shukla U, Malhotra K, Prabhakar T. A comparative study of the effect of clonidine and tramadol on post-spinal anaesthesia shivering. Indian J Anaesth, 2011; 55: 242-246.
6. Shukla U, Malhotra K, Prabhakar T. A comparative study of the effect of clonidine and tramadol on post-spinal anaesthesia shivering. Indian J Anaesth, 2011; 55: 242-246.
7. Dahl JB, Jeppesen IS, Jørgensen H, Wetterslev J, Møiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. Anesthesiology, 1999; 91: 1919–27.
8. Dayer P, Desmeules J, Collart L. Pharmacology of tramadol. Drugs, 1997; 53: 18–24.
9. Alıcı HA, Ku¨rsad H, Gu¨rsan N, Yu¨ksek MS, Cesur M, Dog˘an N. Neurotoxic effects of intrathecal morphine and tramadol in rabbits. EAJM, 2006; 38: 61–7.

10. Alhashemi JA, Kaki AM. Effect of intrathecal tramadol administration on postoperative pain after transurethral resection of prostate. Br J Anaesth, 2003; 91: 536–40.
11. Raffa RB, Friderichs E, Reimann W, et al. Opioid and non-opioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. J Pharmacol Exp Ther, 1992; 260: 275–85.
12. Paar WD, Frankus P, Dengler HJ. The metabolism of tramadol by human liver microsomes. Clin Invest, 1992; 70: 708–10.
13. Carlsson KH, Jurna I. Effects of tramadol on motor and sensory responses of the spinal nociceptive system in the rat. Eur J Pharmacol, 1987; 139: 1–10.
14. Hennies HH, Friderichs E, Wilsman K, et al. Effect of the opioid analgesic tramadol on inactivation of norepinephrine and serotonin. Biochem Pharmacol, 1982; 31: 1654–5.
15. Kayser V, Besson JM, Guildbaud G. Evidence for noradrenergic component in the antinociceptive effect of the analgesic agent tramadol in an animal model of clinical pain, the arthritic rat. Eur J Pharmacol, 1992; 224: 83–8.
16. Choi DH, Ahn HJ, Kim MH: Bupivacaine sparing effect of fentanyl in spinal anesthesia for cesarean delivery. Regional Anesthesia Pain medicine, 2000; 25: 240-245
17. Saifuddin A, Burnett SJ, White J. The variation of position of the conus medullaris in an adult population. A magnetic resonance imaging study. Spine, Jul 1, 1998; 23(13): 1452-6.
18. Broadbent CR, Maxwell WB, Ferrie R, Wilson DJ, Gawne-Cain M, Russell R. Ability of anaesthetists to identify a marked lumbar interspace. Anaesthesia, Nov, 2000; 55(11): 1122-6. [PubMed]
19. Hartmann B, Junger A, Klasen J, Benson M, Jost A, Banzhaf A, Hempelmann G. The incidence and risk factors for hypotension after spinal anesthesia induction: an analysis with automated data collection. Anesth. Analg, Jun, 2002; 94(6): 1521-9, table of contents. [PubMed]
20. Broadbent CR, Maxwell WB, Ferrie R, Wilson DJ, Gawne-Cain M, Russell R. Ability of anaesthetists to identify a marked lumbar interspace. Anaesthesia, Nov, 2000; 55(11): 1122-6. [PubMed]
21. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology, Jun, 1992; 76(6): 906-16. [PubMed]
22. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. Anesthesiology, Oct, 2004; 101(4): 950-9. [PubMed]