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Review article

Assessment of impact of intrathecal magnesium sulfate on bupivacaine-fentanyl subarchanoid block during infraumbilical surgeries: Review

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ABSTRACT

Introduction: Fentanyl has been used intrathecally in various patients in labour.
Aim and Objectives: The main aim of this review article is to establish the addition of magnesium sulfate intrathecally with bupivacaine and fentanyl will enhance the analgesic effect in patient undergoing infraumbilical surgeries.
Methods: We did a literature evaluation in articles like- PubMed, Google Scholar, Web of science etc. The search terms were used for all fields including title, abstracts, keywords and full text. We used Medical Subject Headings (MeSH) and text word terms and tailored the search to individual databases. We used keywords and synonyms to sensitize the search.
Results: For this assessment, we used evaluation of previous studies in Patients receiving 50 mg of intrathecal magnesium sulphate in addition to 12.5 mg of bupivacaine and 25 mcg of fentanyl in subarchanoid block for infraumbilical procedures considerably delay the onset of sensory and motor block as well as the onset of analgesia as compared to the control group. Additionally, this lengthens the time needed to rescue analgesia.
Conclusion: In general thus, we draw the conclusion that there are no appreciable haemodynamic changes or negative effects from adding magnesium to the mixture of bupivacaine and fentanyl administered via the spinal route. The use of magnesium intrathecally as an analgesic in infra umbilical procedures is not well covered in the literature. Therefore, we intended to examine the effects of magnesium in the combination of bupivacaine and fentanyl when administered through spinal route to provide efficient postoperative analgesia that is free from major haemodynamic changes and side effects.
Keywords: Magnesium sulphate, hyperbaric bupivacaine, spinal anaesthesia, Fentanyl

INTRODUCTION

Albert Schwitzer once said, "Pain is a more horrible lord of people than even death itself." One of the main objectives of medical science is the control of pain. Despite all the efforts made to make the intraoperative period pain and stress-free, patients are frequently left to fight for themselves in the postoperative period despite the fact that surgical operations result in severe tissue damage and surgical pain, also known as "post-operative pain," is a universal phenomenon experienced by millions of patients worldwide. The postoperative phase is when the surgical stress response peaks and has a significant impact on practically all systems of the body. Any surgical procedure's morbidity and mortality are unquestionably decreased by a pain-free postoperative phase. In 1898, Karl August Bier made spinal anesthesia available in clinical settings. Even today, a century after its invention, spinal anesthesia is still one of the most often used methods for both elective and urgent surgical procedures, including Caesarean sections, lower abdominal surgeries, orthopaedic treatments, and urological procedures, to name a few. The popularity of the spinal block is mostly due to the block's well-defined end points and the anesthesiologist's reliable ability to produce the block with a single injection. A variety of local anesthetics and additives that enable control over the level, the time of onset, and the duration of spinal anesthesia contribute to the diversity of this type of anesthesia. The amount of neuronal blockage brought on by spinal anesthesia is determined by the distribution of local anesthetic solutions throughout the subarachnoid space.

Since the invention of local anesthetics, various classes of medications have been added as adjuvants to local anesthetics in an effort to prolong

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analgesia and decrease the likelihood of side effects. These medications include epinephrine, opioids, clonidine, neostigmine, ketamine, and benzodiazepines. Fentanyl, a synthetic opioid receptor agonist, is a derivative of phenylpiperidine. Due to its quick onset, short duration, and lower prevalence of respiratory depression, it is chosen as an adjuvant in spinal anesthesia. The most often utilized spinal lipophilic opioid for local anesthetics that lengthen and strengthen the effects of subarachnoid block is fentanyl. By interacting with opioid receptors to activate pain-relieving chemicals, such as endorphins, enkephalins, and dynorphins, opioids imitate the effects of their natural ligands (antinociceptive system). Presynaptic inhibition of neurotransmission (acetylcholine, dopamine, norepinephrine, and dopamine) release causes a decrease in neurotransmission as a result. When given intrathecally, it has a tendency to also not migrate to the fourth ventricle in adequate concentration[1].

It has been demonstrated that using magnesium as an adjuvant to peripheral nerve blocks can also lengthen the time that surgical analgesia lasts. A few clinical studies have looked at the impact of combining anesthetic drugs such bupivacaine with intrathecal magnesium sulphate (MgSO4).The term "physiological calcium channel blocker" refers to magnesium. Magnesium parenterally has been utilized for intraoperative and postoperative analgesia on an empirical basis for a long time. Although systemic magnesium reduces the need for postoperative opioids, its intrathecal usage has also been clinically tested. Magnesium's impact on NMDA receptors is what gives it its analgesic properties[2].

NMDA receptors are voltage-dependently blocked by magnesium. It also has connections to K and Ca ion channels, among others. NMDA channel inhibition is insufficient to efficiently cross the blood-brain barrier and raise cerebrospinal fluid concentrations. The body's fourth most abundant cation and the second most common intracellular cation is magnesium[3]. It is engaged in a wide range of physiological processes, including the activation of enzymes that are involved in energy metabolism, protein synthesis, the control of vasomotor tone, neurotransmission, and signalling. As a pharmaceutical treatment for a number of clinical conditions, including tachyarrhythmia, myocardial and neuronal ischemia, asthma[4].

Our hypothesis is that intrathecal magnesium could enhance opioid spinal analgesia while preventing any adverse effects that could result from using higher intravenous magnesium dosages to examine antinociception modulation in people. The present study was designed In order to determine if intrathecal magnesium sulfate would improve the analgesic efficacy of intrathecal bupivacaine and fentanyl in patients having infra umbilical surgeries[5].

METHOD

The Preferred Reporting Items for Systematic Reviews and Meta-analysis statement served as the instructions for conducting this systematic review. Since all information was gathered from previously published studies, neither patient permission nor ethical review were necessary[6].

SEARCH STRATEGY

We systematically searched for articles and case reports in PubMed, EMbase, Web of science and GOOGLE. We also cross- checked the reference lists and relevant reviews to include additional eligible studies. The search strategy was done using a combination of free text words and Medical Subject Headings (MeSH) terms. Both international and national articles were thoroughly searched and publications related to the use of dexmedetomidine as an adjuvant in labouring patients were included[7].

Inclusion criteria:

The following were the inclusion criteria:

Neuraxial bupivacaine with fentanyl and addition of magnesium sulphate was administered by epidural, intrathecal, route in infraumbilical procedures ,Original and independent studies

Exclusion criteria:

Studies that met one of the following criteria were disqualified:

(1) Non-RCTs, RCT

(2) Conference abstracts, comments to the editor, or studies on animals[8].

Data Extraction

The following data were taken from each article: the first author, the year it was published, the number of cases, baseline patient characteristics, dexmedetomidine, control, study design, the beginning of sensory block, the occurrence of motor block, the duration of sensory block, the duration of motor block, the time to rescue analgesia, the consumption of fentanyl, nausea/vomiting, pruritus, hypotension, bradycardia, neonatal and maternal outcome.

1. The first report of using opioids intrathecally for pain relief in man dates back to 1979. Eight patients with severe, intractable pain in their legs and back as a result of genitourinary tract cancers that had invaded the lumbosacral plexus received intrathecally injected doses of 0.5 to 1.0 mg of morphine. After receiving separate injections of morphine and physiologic saline, two out of the eight patients reported being completely pain-free. After receiving morphine injections, the other six patients said their discomfort was completely gone. Relief continued for an average of 20 hours and for a total of 12 to 24 hours. From the moment the medicine was injected to its maximum effect, it took anywhere between 15 and 45 minutes. The findings impressed the scientists, who recommended more research into this method's potential for treating terminal cancer issues. They also made the assumption that this method might be employed for postoperative pain and obstetric analgesia.
2. In 1987, Hunt CO investigated the use of subarachnoid Fentanyl at the time of cesarean section for perioperative analgesia. Twenty-eight ASA class 1 parturients undergoing elective repeat cesarean section had been studied. With the patient in right lateral decubitus position, a midline subarachnoid injection was performed at the L2-3 or L3-4 interspace. 0ug, 6.25µg, 12.5µg, 25µg, 37.5µg or 50µg of preservative free Fentanyl made to a total volume of 1ml with normal saline was then injected their standard dose of hyperbaric Bupivacine 0.75% in dextrose 8.25%. After injection vital signs, sensory level, motor block, pain score and presence or absence of pruritus, nausea, dysphoria recorded. Apgar scores maternal vein and umbilical cord blood gases were obtained at the time of delivery. They concluded that the onset or extent of subarachnoid block did not differ irrespective of different increased concentration of Fentanyl and Subarachnoid Fentanyl significantly improved both intraoperative and postoperative analgesia when administered prior to Bupivacaine 0.75%. 6.25µg appeared to be capable of producing the same analgesia as larger doses, with decreased incidences of side effects.
3. In 1989, Hunt et alevaluated the potential of Fentanyl administered in subarachnoid space to improve intraoperative and perioperative period. Injection of Fentanyl 0µg, 2.5µg, 5µg, 6.25µg, 12.5µg, 25µg, 37.5µg or 50µg to make a total volume of 1 ml (by adding normal saline) to subarachnoid space followed by administration of dose of 0.75% Bupivicaine in 8.25% Dextrose according the height of patient undergoing cesarean section. They found that no significant differences in the onset time of sensory motor block.and number of segments regressed at 60 minutes was prolonged.and with addition of 6.25µg of Fentanyl, complete analgesia was increased. Their study concluded that the addition of > 6.25µg Fentanyl to hyperbaric Bupivacaine for spinal anesthesia in parturients undergoing cesarean section improved intraoperative as well as immediate post- operative analgesia with no adverse effect on mother or neonate.
4. Respiratory depression and spinal opioids etches RC et al in 1989 did a review study of all the previously done studies on intrathecal opioids and came to a conclusion that administration of epidural and intrathecal opioids provided excellent postoperative analgesia, but a minority of patients suffered dangerous respiratory depression[9].
5. In 1993,Wang C et al conducted a study on dogs to examine specific enhancement by fentanyl, of the effects of intrathecal Bupivicaine on nociceptive afferent but not on sympathetic efferent pathway. They also examined interaction with Fentanyl. They concluded that intrathecal Bupivicaine had no selectivity for the efferent and afferent pathways and intrathecal Fentanyl acts synergistically to enhance the effects of Bupivacaine on the

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afferent pathway without a measurable effects on sympathetic outflow[10].

6. Niemi et al compared intrathecal morphine bolus with intrathecal fentanyl infusion in 1993 to treat post-operative pain following hip arthroplasty. The study involved sixty individuals who were scheduled for hip replacement surgery. Plain 0.5% Bupivacaine in 2mL doses was used to establish spinal anaesthesia. As needed, more Bupivacaine was administered in 0.5-mL doses. Patients received 0.5 mL of saline as a single bolus, followed by an infusion of 120 g of fentanyl over the course of 24 hours (Group I, n = 20), 0.5 mL of saline, followed by an infusion of 200 g of morphine over the course of 24 hours (Group II, n = 20), or 200 g of morphine as a single bolus, followed by an infusion of 3ml. They came to the conclusion that fentanyl intrathecal infusion at 5 g/hr, initiated along with bupivacaine spinal block, was insufficient for post-operative analgesia following hip surgery in older patients. Better analgesia was achieved with intrathecal morphine (200 g), either as a single dosage or as a continuous infusion[11].
7. The impact of intrathecal fentanyl in lower extremity revascularization procedures was investigated in 1994 by Reuben S. S. et al. With the use of a continuous spinal approach, surgical anesthesia was induced. Antiemetics or opioids were not given to any patients before surgery. Patients received either 0, 5, 10, 20, 40, or 50 g of fentanyl via the spinal catheter postoperatively after the spinal anesthetic had completely subsided. According to the findings, 40 mg of intrathecal fentanyl offers older patients enough analgesia for about 5 hours with a low frequency of adverse effects[12].
8. In 1994, Simpson et al investigated the effect of intrathecal magnesium sulphate in dogs after minor thoracotomy incision thoracic aortic cross clamping and came to the conclusion that intrathecal magnesium sulphate can avoid spinal cord injury. No ischemic or neurological impairment was visible in any of the histological samples taken from the dogs that received magnesium. The safety profile of intrathecal magnesium sulphate is further demonstrated by this investigation.
9. One of the early investigations demonstrating the anti nociceptive properties of magnesium was carried out by Tramer MR et al in 1996. 42 ASA I and II patients undergoing abdominal hysterectomy were included in their randomized double-blind research. Before the procedure began, the study group was given 15 ml of 20% magnesium, and then got 2.5 ml per hour for the following 20 hours. The equivalent amount of ordinary saline was given to the control group. Up to the 48th postoperative hour, one week, and one month after surgery, pain at rest and at peak expiratory flow as well as discomfort were assessed. After the first and second postoperative nights, insomnia was assessed. They came to the conclusion that the use of magnesium sulphate before to surgery was not only related with no negative effects but also a lesser need for analgesics, less discomfort, and improved postoperative sleep quality.
10. A randomized double blind study was conducted in 1998 by Koinig H, et al on 46 ASA I and II patients undergoing knee arthroscopy under complete intravenous anesthesia. The patients either received the same amount of isotonic sodium chloride solution or 50 mg/kg of magnesium sulfate preoperatively and 8 mg/kg/hr during surgery. Propofol (2 mg/kg for induction, 6-8 mg/kg/hr for maintenance), fentanyl (3 g/kg for induction), and vecuronium (0.1 mg/kg for intubation) were used to administer i.v. anesthesia. A bolus of fentanyl (1-2 g/kg) was administered to manage intraoperative pain, which was defined as a rise in mean arterial blood pressure and heart rate of more than 20% from baseline values following the induction of anesthesia. Fentanyl (0.5 g/kg) was used to achieve postoperative analgesia, which was monitored for 4 hours using the pain visual analog scale.

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DISCUSSION

For procedures involving the lower abdomen, the perineum, and the lower extremities to make them painless, spinal anesthesia, which is the temporary interruption of nerve transmission within the subarachnoid space and has been successfully and widely used for almost 100 years after an injection of a local anesthetic solution into cerebrospinal fluid, has many potential advantages over general anesthesia. Local anesthetics like lignocaine and bupivacaine are frequently used to block the spinal subarchnoid space. One drawback of spinal anesthesia with local anesthetics only is that analgesia terminates when the block regresses, resulting in an early post-operative requirement for analgesics. In addition to being uncomfortable, post-operative pain can have other negative effects, mostly on the cardio-respiratory system.

Intrathecal adjuvants: Adjuvants are drugs that, when used with local anesthetics, lengthen the duration of analgesia, thereby extending post-operative analgesia, decreasing the need for post-operative analgesics, promoting early ambulation, and shortening the length of hospitalization. Major technological advances in postoperative analgesia have been made over the past ten years. Since the N-methyl-d-aspartate (NMDA) receptors were discovered, along with their connections to the transmission of nociceptive pain and central sensitization, NMDA receptor antagonists have been crucial in the fight against central sensitization of pain[13].

In reaction to unpleasant stimuli, glutamate and aspartate neurotransmitters are released, and they bind to the NMDA receptors as well as many other excitatory amino acid receptors. When NMDA receptors are activated, the cell experiences calcium and sodium inflow, potassium efflux, and the beginning of central sensitization[14].

Magnesium intrathecally:

No appreciable amount of magnesium administered intravenously (6 g followed by a 2-g/h infusion) passes the blood-brain barrier. The authors were able to show a negative correlation between the study group's painkiller usage and CSF magnesium levels. Thus, Buvendran et al. hypothesized that intrathecal magnesium injection could enhance opioid spinal analgesia without having to provide higher dosages intravenously, which might be necessary to see antinociceptive modulation in people. This was the justification for administering magnesium intravenously.

Administration of intrathecal magnesium sulfate is safe because there is currently no medicine that can be used as an adjuvant to spinal bupivacaine that precisely decreases nociception without the attendant adverse effects. This study will assess the impact of combining intrathecal magnesium sulphate with bupivacaine-fentanyl subarchanoid block during infraumbilical procedures.Human liver microsomes and recombinant CYP3A4 catalyze the majority of the drug's metabolism.

Choice of magnesium sulphate with LA intrathecally:

Magnesium is also known as the natural NMDA receptor antagonist and as the physiological calcium channel blocker. Magnesium blocks NMDA channels in a voltage-dependent manner, significantly reducing NMDA-induced currents. Magnesium sulphate cannot effectively modulate antinociception by NMDA channel antagonism via parenteral administration due to limited blood-brain barrier penetration. No appreciable quantity of magnesium passes the blood-brain barrier, even when administered intravenously in massive quantities (6 g followed by an infusion of 2 g/h). Magnesium administered intravenously may be too toxic to see antinociceptive modulation in people, therefore intrathecal magnesium may be able to enhance opioid spinal analgesia without having the same negative side effects. When given to anesthetic agent intrathecally, various adjuvants have varying effects on the onset, duration, and degree of block obtained. Contrary to intrathecal adjuvants such magnesium sulphate, it has been observed that the beginning of sensory and motor block occurs relatively quickly with intrathecal midazolam. When the length of post-operative analgesia was examined, intrathecal magnesium sulphate was found to be more effective than midazolam[15].

Non-competitive NMDA receptor antagonists bind and dissociate very slowly, which might be why anesthesia was maintained postoperatively and less postoperative analgesia was needed. The absence of central side effects following systemic administration of high doses of magnesium and the possible postoperative opioid-sparing effects of magnesium are likely due to a localized action of intrathecal magnesium sulphate on spinal nociceptive pathways. The risk of respiratory depression is correlated with the use of intrathecal opioid. The lipid-soluble opioid fentanyl, in contrast to the less lipid-soluble

morphine, binds to opioid receptors in the dorsal horn of the spinal cord very quickly, leaving only limited amounts of material for cephalad migration to the fourth ventricle. To have an effect on the dorsal horn of the spinal cord, fentanyl binds to opioid receptors. According to Varassi et al 25 mg of fentanyl administered subarachnoidly during spinal anesthesia in unprescribed men did not result in early respiratory depression in geriatric patients[16].

CONCLUSION

With diligent assessment of patient's vitals and correct patient selection, magnesium sulphate may be utilized as a neuraxial adjuvant in nfraumbilical surgeries. We systematically searched for articles, case reports in PubMed, Embase, Web of science and GOOGLE. We also crosschecked the reference lists to include extra information related to article. The plan of action for this study was done by using (MeSH) terms, Medical Subject Headings. We have included international and national articles and publications based on effect of dexmedetomidine as an analgesic in pregnant females in labour. Various studies have shown that this dexmedetomidine does not cross the utero-placental tissue but still the patient selection for its use in labour analgesia by an anesthesiologist must be done carefully. If hepatic or renal impairment is present, then dose should be adjust accordingly. When dexmedetomidine is used within the adjustable dose range, psychomotor function preservation is seen among patients along with improve and may improve parturients efforts during labour. When compared with opioids as an adjuvants and involving placebo labouring patients without any adjuvant, dexmedetomidine proves to be better adjuvant when used with spinal or epidural local anaesthetics, with better analgesic action than placebo and showing similar pain control like- opioids during labour, without major side- effects on the mother and foetus, and also reduction in repeated requirement of epidural doses seen with good safety profile for both parturients and foetus.

Dexmedetomidine when used in combination with local anaesthetics to relieve pain during labour and delivery proves to be safe, effective, dependable, inexpensive, and acceptable technique of pain treatment. Thus the significant message that can be concluded is the satisfactory result of the drug, providing adequate analgesia when used in labouring parturients.

LIMITATIONS:

- Serum magnesium levels of patients were not performed pre-operatively .
- Duration of the surgery is not mentioned which may interfere with effect of the drug and comparison between the two groups .
- Different dosages of MgSO4 was not studied .
- Effect on pH and baricity of local anesthetic on addition of magnesium sulphate to bupivacaine fentanyl was not studied .
- Magnesium sulphate was not studied only with bupivacaine but was studied only in combination with bupicaine and fentanyl .
- The pharmacokinetics of spinal bupivacaine may change if intrathecal MgSO4 is added, leading to a more rapid clearance of bupivacaine in the current study.

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