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A Comparisoin of Fentanyl Citrate and Magnesium Sulphate as Adjuvants to 0.5% heavy Bupivacaine in Spinal Anaesthesia

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Abstract

Spinal anaesthesia is preferred regional anaesthesia technique in lower abdominal surgeries. Advantages are conscious and spontaneously breathing patient [25], good muscle relaxation, cost effectiveness and adjuvants injected intrathecally prolong the anaesthetic effects [26,27]. *Aim of the study:* To compare Fentanyl Citrate and Magnesium sulfate as adjuvants to 3 ml of 0.5% bupivacaine in infraumbilical surgeries under spinal anaesthesia, about onset and duration of sensory and motor block, intraoperative hemodynamics, postoperative pain and side effects. *Materials & Methods:* After Institutional ethics committee approval, a double-blinded comparative study was conducted in 100 patients at Osmania General hospital during 2014-2017. Patients were divided into two groups of 50 no.'s each Group F- 3 ml 0.5% Heavy Bupivacaine & Fentanyl citrate 25 mcg, Group M –3 ml 0.5% Heavy Bupivacaine & $MgSO_4$ 100 mg were deposited intrathecally. Intraoperatively Sensory and Motor block onset and duration, HR, SBP, DBP & MAP, SpO_2, side effects were assessed. *Results:* In group M– onset of sensory and motor block is significantly prolonged , duration of analgesia, motor block is comparable to group F and patients in group M were hemodynamically stable perioperatively, and at end of 24 hrs postoperatively VAS score was ≥ 3 at indicates a quality post operative analgesia. *Conclusion:* Fentanyl citrate as adjuvant to 0.5% heavy bupivacaine effectively augmented quality of spinal anaesthesia; its advantages are limited by incidence of side effects. $MgSO_4$ 100 mg provides excellent perioperative analgesia and stable hemodynamics and is an attractive non-opioid adjuvant alternative to fentanyl.

Keywords: Adjuvants; Local anaesthetics; Magnesium sulfate; NMDA receptors; Opioids; Spinal anaesthesia.

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Introduction

Anaesthesiologists in present day practice are also involved in effective post-operative pain management. Spinal anaesthesia is choice of anaesthesia technique in infraumbilical surgeries as it is safe and faster onset of surgical anaesthesia, provides excellent operating conditions and is economical [30]. Adjuvants [32,33] added to local anaesthe -tics act synergistically to enhance quality of spinal anaesthesia i.e., prolonged duration of sensory and motor block and effectiveness of spinal analgesia thus eliminating intra and post-operative pain [38,40]. Local anaesthetic adjuvants include

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a wide array of drugs with different mechanisms of action eg., opioids, epinephrine, alpha-2 adren -ergic agonists, steroids, anti-inflammatory drugs, midazolam, ketamine, magnesium sulfate and neostigmine. The advantage of combining two types of agents is explained by different analgesic properties and their ability to block pain at two different sites. Opioids specifically bind and activate opiate receptors in substantia gelatinosa produce analgesia and by systemic absorption whereas local anaesthetics provide analgesia by blocking impulse transmission at nerve roots and dorsal root ganglia. Intrathecal opioids enhance sensory and motor block [45] and potentiate anti-nociception by G protien coupled receptor mechanisms and hyperpolarisation of afferent sensory neurons. Buprenorphine, Fentanyl, Sufentanyl and Afentanil [49,50] are commonly used opioid adjuvants. The dose, lipophilicity and acid-base milieu of site of drug deposition determine extent and efficacy of block [54]. Fentanyl citrate a lipophilic synthetic phenylpiperidine, μ- mu, κ-*kappa* receptor agonist, is used intrathecally in dose range of 10-25 μg has rapid onset of action strongly binds to plasma proteins, potentiates afferent sensory block in terms of onset, duration and extent of analgesia. Its effects are limited by incidence of hemodynamic instability and side effects -respiratory depression, ponv, vomiting and pruritus [29] etc.

NMDA (N-Methyl-D Aspartate) receptor channels are ligand-gated ion channels involved in pain processing, generate slow excitatory postsynaptic currents at glutaminergic synapses. A sustained NMDA receptor activation promotes intracellular signaling that results in long-term synaptic plasticity, wind-up phenomenon and central sensitization. These events determine duration and intensity of postoperative pain. Mg^{2+} and Ketamine prevent central sensitization and reduce postoperative analgesic requirements [58,59,60–61]. Mg^{2+} has antinociceptive effects by a non-competitive NMDA receptor antagonism in spinal cord [79] and its effects are based on, regulation of calcium influx [1]. Intrathecal Mg^{2+} 50 mg [2,3] decreased postoperative analgesic [4] requirements by almost 50%. Mg^{2+} may have a pre-emptive analgesic action and Epidural Mg and bupivacaine decrease pain scores and analgesic requirements for up to 72 hrs [5] without any increase in systemic side effects [6]. Although $MgSO_4$ prolongs spinal anaesthesia, it may fail to reduce bupivacaine dose requirement [8]. various options are being extensively evaluated as alternative to opioids.

Role of Magnesium in Anaesthesia

Magnesium an intrinsic component of many adenosine 5'-triphosphatases, acts as an endogenous calcium antagonist by noncompetitive inhibition of inositol triphosphate-gated Ca^{2+} channels [1,4] i.e., 'natural physiological calcium antagonism'. It is an endogenous regulator of several electrolytes [3], has modulatory effects on Na, K currents and influence membrane potential [5,6]. Its antinociceptive effects are due to NMDA glutamate receptor antagonism [7-10] and inhibition of catecholamine release. It was observed during anaesthesia serum Mg^{2+} conc. decrease and return to normal 1-3 days postoperatively [12]. Mg^{2+} has potential benefits in anaesthesia [3] and is proposed as anaesthetic, along with volatile anaesthetic agents has super additive effect at central NMDA-aspartate receptors, inhibit glutamate/glycine signaling function [24] and decrease MAC, enhance analgesia and muscle relaxation and improves patient outcomes. Many authors have studied role of $MgSO_4$ as adjuvant for providing intra and postoperative analgesia [10,1,23]. Tramer MR et al. [1]., performed a randomized, double blind study to assess effect of Mg as physiologic NMDA antagonist on analgesic requirements, pain and quality of sleep in postoperative period. Sakuraba et al. [15]., magnesium reduces catecholamine release during intubation, decreases succinylcholine induced fasciculation and may prevent hyperkalemia [14,16]. Turan et al. [18] Mg^{2+} added to lidocaine has beneficial effects in terms of improved quality of IVRA (Bier block), shorter onset times of sensory and motor blocks and better postoperative analgesia. It can be an useful analgesic adjunct in TIVA (Seyhan et al.) reduces propofol, atracurium and postoperative morphine consumption in gynecologic surgeries and concluded that it improves quality of postoperative analgesia and decreases PONV [19], due to lower consumption of volatile anesthetics (sevoflurane) [2]. Arcioni et al. [20] investigated synergistic interactions between intrathecal administration of magnesium sulfate and anaesthetics in terms of postoperative analgesia. Mg^{2+} reduces propofol, rocuronium and fentanyl in spinal surgical patients Gupta et al., [22], its use intraoperatively may decrease remifentanil-induced hyperalgesia. Mg^{2+} is effective in treatment of intra and post-operative pain an important component of postoperative recovery as it serves to blunt autonomic, somatic and endocrine reflexes with a resultant potential decrease in perioperative morbidity. Bupivacaine is most commonly used amide local anaesthetic in spinal anaesthesia, it is a white crystalline powder soluble inwater, with pH

of 5.2 and sp.gravity of 1.021 is available as 0.5% hyperbaric solution in 8% dextrosefor intrathecal use.

Aim & Objectives of the Study

To study and compare effects of Fentanyl citrate and Magnesium sulphate as adjuvant to intrathecal 0.5% heavy bupivacaine in 100 patients posted for infraumbilical surgeries, during study the following spinal anaesthesia characteristics were compared between two groups.

1. Onset and duration of Sensory Analgesia – Speed of onset and duration of analgesia.
2. Onset and duration of Motor Blockade – Speed of onset and duration of motor blockade.
3. Intraoperative Hempdynamic changes, Sedation and side effects.
4. Post operative pain assessed by Visual Analog Scale (VAS).

Materials and Methods

After Institutional Ethics Committee approval study was carried out at Govt. Maternity Hospital and Osmania General Hospital during 2014-2017, 100 randomly selected patients in age group of 18-55 yrs belonging to ASA I & II of both sex were included in study, patients were posted for infraumbilical surgeries (Ovarian cystectomy, Hysterecomy, Sac Eversion, Inguinal hernioraphy, Appendectomy, Cystolithotomy and Ureterolithotomy) under spinal anaesthesia. Pre-anaesthetic assessment done to screen and evaluate major systemic illnesses, informed consent was obtained from all patients include in study, they were explained about spinal anaesthesia procedure and educated about using *'visual analog scale'*. Patients were randomized into 2 groups based on adjuvant drug received intrathecally.

(i). Group F (n=50) -3 ml 0.5% heavy Bupivacaine + Fentanyl 25 µgm.

(ii). Group M (n=50) -3 ml 0.5% heavy Bupivacaine 0.5% +100 mg $MgSO_4$.

Patients were fasting overnight and pre-medication included tab. alprazolam 0.5 mg at bed time, tab. rantidine 150 mg at bed time and morning before surgery. On day of surgery, anaesthesia equipment checked and emergency drugs were kept ready, on arrival of patient at OR multiparameter monitor (Philips Suresign VM8) was connected and baseline vitals were recorded, 18G i.v. access secured on left forearm and all patients pre-loaded 10 ml/kg of RL15 mins prior to surgery.

Inclusion Criteria

(i) ASA physical status I & II

(ii) Age 18 to 60 yrs

Exclusion Criteria

(i) ASA Gr. III & IV

(ii) Infection at site of injection

(iii) Coagulopathy

(iv) H/o Local Anaesthetic sensitivity

Under aseptic precautions all patients received spinal anaesthesia in right lateral position at L_3-L_4 interspinous space with 26G Quincke Babcock short bevel spinal needle, after obtaining clear CSF flow with needle bevel directed cephalad, local anaesthetic and adjuvant drugs were deposited intrathecally over a period of 10 seconds. Intraoperatively, following spinal anaesthesia characters were recorded and entered into data sheet for statistical analysis.

(i) Time of onset of sensory block of T_8 level using pin prick method.

(ii) Time of onset of motor block - Bromage scale 3 assesed by Modified Bromage scale.

Modified Bromage Scale for Assesing Motor Block
Bromage 0 – Able to move hip, knee and ankle.
Bromage 1 – Unable to move hip, able to move knees and ankle.
Bromage 2 – Unable to move hip, knees but able to move ankle.
Bromage 3 – Unable to move hip, knee and ankle.

(iii) Duration of Analgesia.

(iv) Duration of motor block.

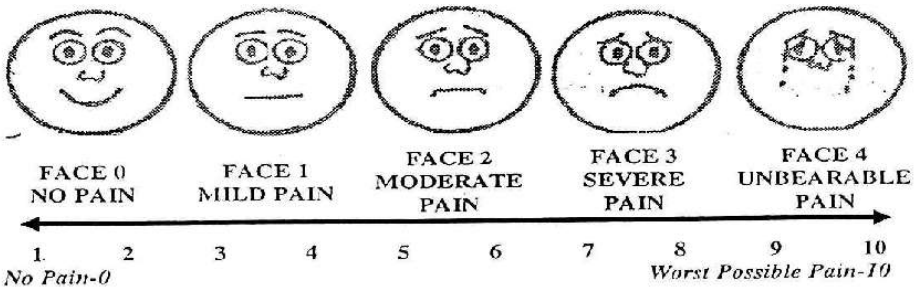
(v) Intraoperative Hemodynamics-HR, NIBP (SBP, DBP & MAP) & SpO_2 recorded every 5 mins for first 50 mins and every 10 mins till end of surgery.

(vi) Post operative sedation assessed by "*Modified Ramsay Sedation Score'* and side effects.

(vii) Postoperative pain assessed by "*Visual Analogue Scale.*"

Modified Ramsay Sedation Scale		
1	=	Agitated, restless
2	=	Cooperative, tranquil
3	=	Responds to verbal commands while sleeping
4	=	Brisk response to glabellar tap or loud noise while sleeping
5	=	Sluggish response to glabellar tap or loud noise while sleeping
6	=	No response to glabellar tap or loud noise while sleeping

Visual Analog Scale

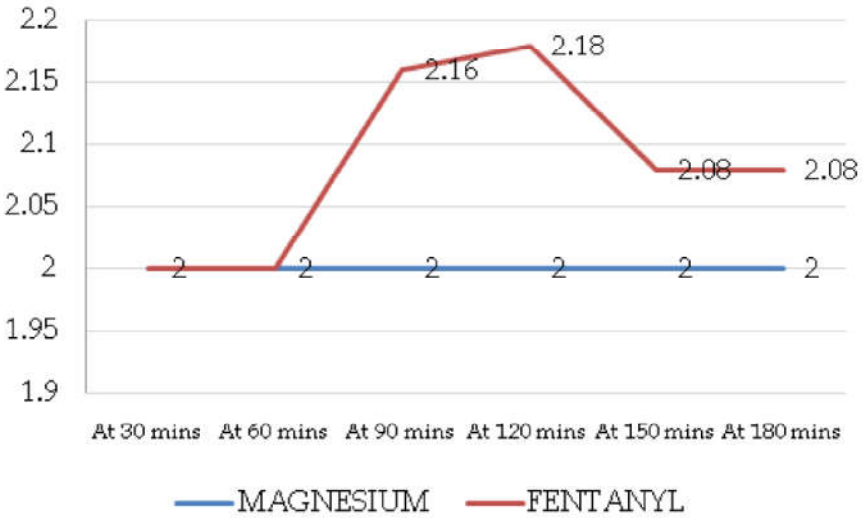


Postoperatively patients marks line on VAS to indicate pain intensity, supplemental analgesia was given for VAS score > 3 and time for analgesia supplementation was noted. Intra-operatively hypotension defined as fall in blood pressure of >20% fall from baseline MAP and treated with 0.9% NS 200 ml bolus infusion and 6 mg ephedrine i.v. Bradycardia HR<50 beats per minute was treated with 0.5 mg atropine iv. Respiratory depression defined as RR< 9 breaths/min, SpO_2 < 90% on room air. Post operatively time for 2 segement regression of sensory block and motor block to reach Bromage scale 3 to 0 were also noted.

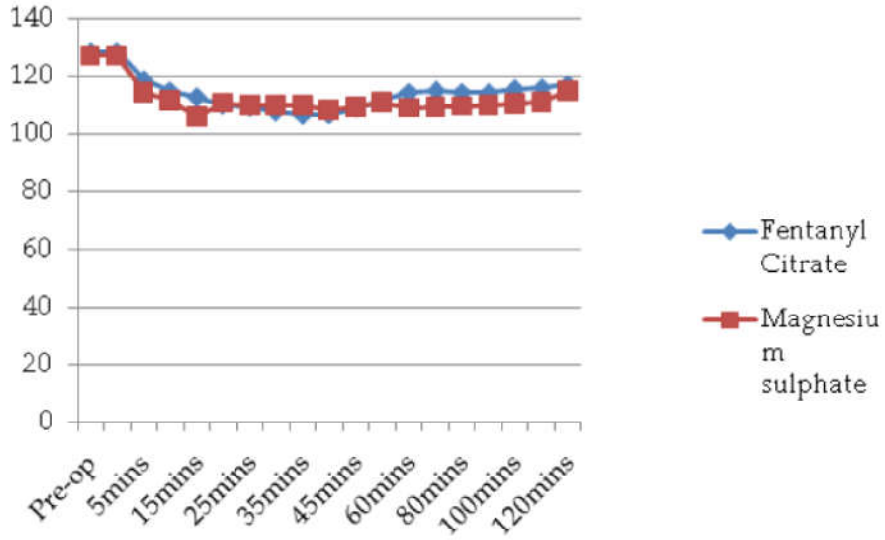
Observations and Results

Table 1: Spinal Anaesthesia Characteristics

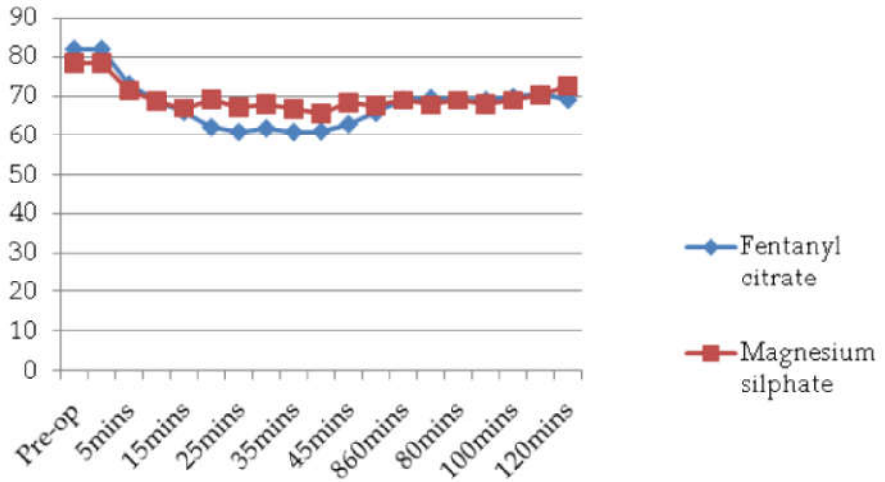
	Group F (n=50)	Group M (n=50)	'p' value
Maximum sensory level attained (n[%])			
T4	18/50(33%)	6/50 (12%)	0.042
T6	22/50	24/50	0,042
Onset to T8	2.280 + 0.50	5.63 + 0.94	0.001
Duration of Analgesia	427±46.86	365.0 + 45.99	0.001 (S)
Onset of Motor block (Modified Bromage Scale 3)	3.95 + 5.23	6.420 + 0.69	0.01
Duration of Motor block	323.92 + 48.64	278.20 + 36.67	0.001 (S)
Post-op VAS			
Post-op 2nd hours	1.04+-0.19	1.18+-0.4	0.0001(HS)
Post-op 6 hours	2.3 ±0.78	3.06±1.008	0.000 (S)
Post-op 12 hours	3.2±0.69	3.66±0.71	0.000 (S)
Post-op 24 hours	3.32±0.61	3.68±0.96	0.02(S)
First pain	427.24 + 46.86	365.00 + 45.99	0.000 (HS)
Post operative sedation (at 2 hrs)	2.18 ± 0.38	2	0.001(S)



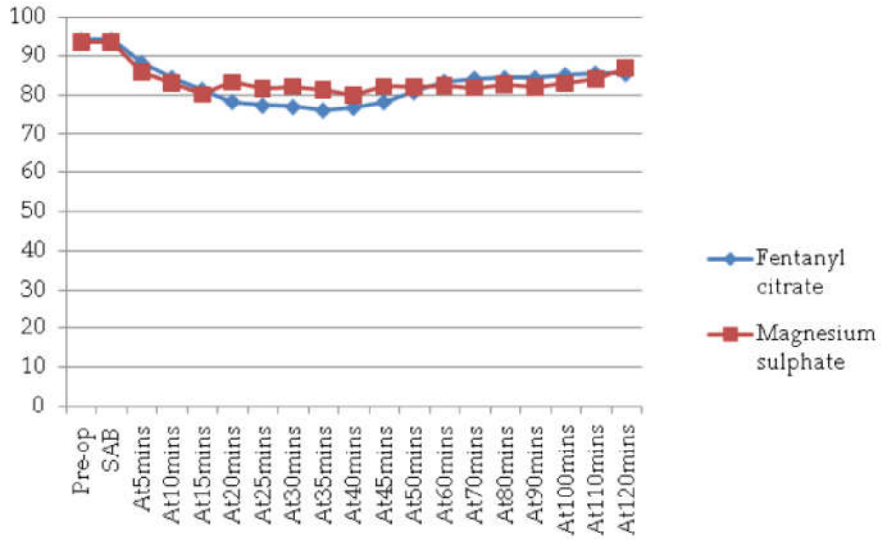
Graph 1: Modified Ramsay Sedation Score



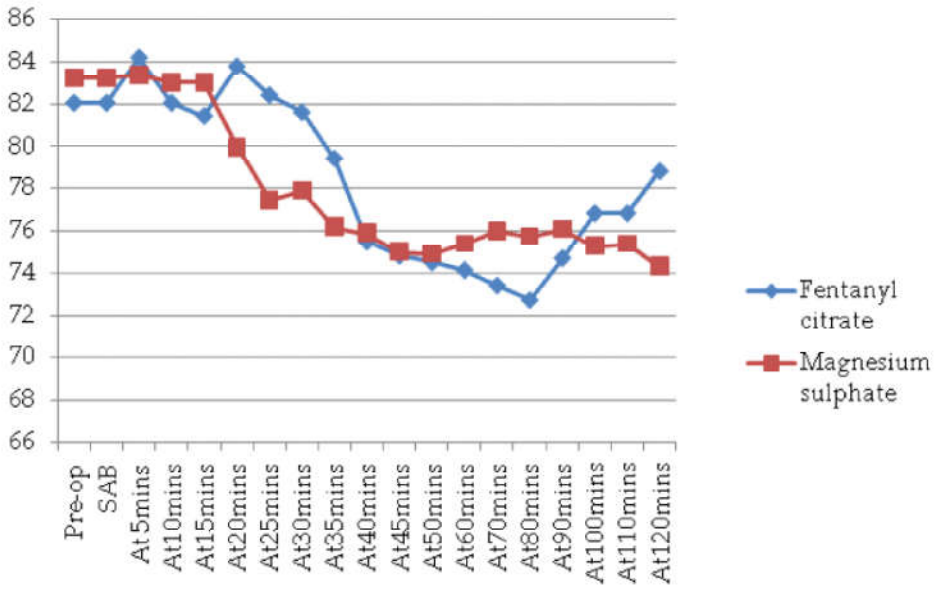
Graph 2: Changes in Systolic Blood Pressure



Graph 3: Changes in Diastolic Blood Pressure



Graph 4: Changes in Mean Arterial Pressure



Graph 5: Changes in Heart rate

Table 2: Side effects of adjuvant drugs in both groups

	Group F, Fentanyl (n=50) (n[%])	Group M, MgSO4 (n=50) (n[%])
No side effects	30 (60%)	42 (84%)
Bradycardia	0	8 (16%)
Hypotension	14 (28%)	0
Nausea	2 (4%)	0
Pruritis	3 (6%)	0
Vomiting	1 (2%)	0

Chi square = 25.0, df = 5, P value = 0.001 (S)

Statistical Methods [47,48]

Descriptive statistical analysis was carried out; results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements as percentage (%). Significancies assessed at 5% level of significance. Statistical analysis was done by applying Chi-Square test, Anova test and Students 't' test and p value determined, $p > 0.05$-not significant, $p < 0.05$ is significant, $p < 0.001$is highly significant.

Discussion

The aim of post operative pain relief is provision of subjective comfort and inhibition of surgical trauma induced nociceptive impulses, neuroendocrine responses and facilitate early functional recovery. Central sensitization is the mechanisms implicated in persistence of postoperative pain, which is dependent on activation of dorsal horn NMDA receptors by excitatory amino acid transmitters - aspartate and glutamate. A continuous search is on for newer methods to augment quality of spinal anaesthesia and prolong duration of analgesia, adding adjuvants to local anaesthetics deposited intrathecally is a method gaining popularity, is said to eliminate intra and postoperative pain. Opioids are mainstay of perioperative pain management have a dose dependent effect on duration of postoperative analgesia and are associated with significant side effects. Fentanyl has faster onset of analgesia due to its lipophilic properties and provides better intra and early post operative pain relief but has disadvantages - hemodynamic instability and systemic side-effects. NMDA antagonists have a synergistic interaction with local anaesthetics and prolong postoperative analgesia [75,76]. Study by Dayioglu et al. [74] proved addition of Mg^{2+} to local anesthetic increases duration of spinal analgesia [60,61].

Opioids use is said to be associated with immunomodulation, inhibition of pro-inflammatory cytokines, induction of long term hyperalgesia, neuroplastic changes in CNS, increase NMDA receptor activity resulting in opioid tolerance. In *vitro* studies have shown that Mg^{2+} significantly inhibited endotoxin-induced up-regulation of inflammatory molecules and NF-kB, by inhibiting L-type calcium channels. Ketamine and Mg^{2+} as NMDA receptor antagonist prevent occurrence and recurrence of all opioid induced phenomena. Koining reported intravenous Mg^{2+} significantly decreases fentanyl consumption in peri and post-operative periods, may act as an analgesic adjuvant (McCartney et al., 2004).

Khalili GI, Janghorbani M et al. [56,57]., 100 mg of $MgSO_4$ added to 15 mg of 0.5% heavy bupivacaine hcl with out opioids significantly prolonged duration of sensory block and onset of spinal anaesthesia.,

Sudharshan Kumar et al. [58] concluded intrathecal Magnesium sulfate (100 mg) as an adjuvant prolongs duration of analgesia and decreases demand for rescue analgesics than 50 mg.[34] $MgSO_4$ @100 mg dose or Fentanyl 25 µg as adjuvants to intrathecal 0.5% heavy bupivacaine significantly prolongs duration of analgesia, $MgSO_4$ provides better haemodynamic stability with fewer side effects., Sarika Katiyar, Chhavi Dwivedi et al. [59].

Beigomkhezri et al. [60] concluded $MgSO_4$ (50 mg) along with 0.5% heavy bupivacaine significantly prolonged onset of both sensory and motor blockade compared with fentanyl. Rajesh vasure et al. [62]., concluded intrathecal bupivacaine along with 50mg $MgSO_4$ results in significant prolongation of duration of analgesia with a more stable hemodynamic profile and lesser side effect and onset of sensory block was significantly delayed. Syed aliaasim et al concluded, (100 mg) magnesium sulphate or (25 µg) fentanyl as adjuvants to 0.5% heavy bupivacaine to spinal anaesthesia. With magnesium, in Group BM there was slower ascent of drug, probably due to change in baricity of drug. Analysis of intra-operative haemodynamics showed that the incidence of hypotension and bradycardia was more in fentanyl group as compared to magnesium group [61].

Very few studies are available describing pros and cons regarding each adjuvant, present clinical study was undertaken on basis of evidence shown above, it is suggested that magnesium may be a useful adjuvant to opioids for spinal anesthesia [62]. Intraoperatively spinal anaesthesia characteristics and hemodynamic parameters have been observed, compared and analysed between fentanyl citrate and magnesium sulphate groups in terms of efficacy and safety as intrathecal adjuvants.

In present study, onset of T_8 level sensory block with fentanyl (25mcg) is faster 2.280±0.50 mins and $MgSO_4$ (100 mg) is 5.63±0.94 mins, the onset time statistically significant with 'p' value of 0.001. The maximum height of sensory level T_4 was achieved in 36% of patients in group F(n=18) and 12% of patients in group M (n=6) with 'p' value of 0.042 is significant statistically. Motor block onset time- bromage scale 3 in group F-3.9 mins±0.23 and group M-6.4 mins±0.69 statistically significant with 'p' value of 0.01.

The delay in onset results in our study are in accordance with studies by Rajesh vasure et al., a T4 sensory level with $MgSO_4$ 50 mg a was achieved in 4.45 mins, fentanyl 25 mcg in 1.62 mins. In study by Beigom et al., sensory level of T10 was achieved in 5.86 mins ($MgSO_4$ 50 mg), 1.46 mins (fentanyl 25 µg) it is evident from above studies that $MgSO_4$ delayed the onset of sensory block compared to fentanyl. It is evident that $MgSO_4$ delayed onset, this could be explained that slower ascent of drug is probably due to changes in baricity of spinal drug [59].

The duration of analgesia in our study was - group F (fentanyl 25 mcg) 427±46.86 mins group M (100 mg) -365±45.99 mins, difference in duration of analgesia is statistically significant with 'p' value of 0.001(S), duration of motor block in group F - 323.92 ±48.64 mins and group M - 278.20±36.67 mins, the difference between two groups was statistically significant with 'p' value of 0.001 (S). In this study we found fentanyl (25 µg) as adjuvant prolonged duration of analgesia -427.24±46.86 mins in comparision with $MgSO_4$ -365.0±45.99 mins, Mg^{2+} shorter duration of analgesia may be due to increase in bupivacaine's metabolism by activation of cytochrome P 450.

Khalili G, Janghorbani M et al. study duration of analgesia was significantly longer with 100 mg Mg^{2+} is 178 mins compared to control group (normal saline) 167.4 mins. In Sarika Katiyar, Chhavi Dwivedi et al. study duration of analgesia was significantly longer 374.37 mins with 25 µg fentanyl compared to 100 mg $MgSO_4$ 328.13 mins. Syed aliaasim et al., duration of analgesia with 25 µg fentanyl -377 mins as compared to $MgSO_4$, 100 mg 326 mins. Rajesh vasure et al. duration of analgesia was significantly longer with Fentanyl 25 µg -238 mins as compared to spinal $MgSO_4$, 50 mg -164 mins. In Beigom et al., study duration of analgesia with intrathecal fentanyl 25 µg -183 mins as compared to intrathecal $MgSO_4$ (50 mg) -133 mins, duration of motor block $MgSO_4$-118 mins and Fentanyl-171 mins. In Sarika Katiyar, Chhavi Dwivedi et al. duration of motor block with 100 mg $MgSO_4$ is 228 mins as compared to 291 mins with 25µ fentanyl. It is observed in above studies higher doses of $MgSO_4$ prolongs duration of analgesia.

In present study 100mg of magnesium sulphate and fentanyl 25 µg were taken as adjuvants to 0.5% heavy bupivacaine to study effects on spinal anaesthesia, the findings were fentanyl prolongs duration of analgesia and duration of motor block compared to $MgSO_4$, the hemodynamic parameters were compared between two groups it was observed that incidence of hypotension was

28% of patients in group F and none in group M which was statistically significant with 'p' value of 0.001, results were similar to observations made in the studies by Syed aliaasim et al. (19% decrease) and Sarika Katiyar, Chhavi Dwivedi et al. (20% decrease). The absence of hypotension in group M may be attributable to gradual onset of sympathetic blockade, bradycardia was found in 16% of patients in Mg^{2+} group, similar to observations made in Hemalatha et al study.

The incidence of side effects were compared, patients in group F experienced nausea (n= 2, 4%), vomiting (n=1, 2%) and pruritis (n=3, 6%) in group M- no ponv, the observations were similar lines to study by Rajesh vasure et al. The absence of nausea, vomiting and shivering in group M ($MgSO_4$), could be explained due to propable inhibitory action on nausea and vomiting and it decreases the incidence of shivering . The post-operative pain was measured by VAS scale, group F had lower VAS scores at 2, 3, 4, 6, 12, 24 hrs, the time taken for first request of analgesia with fentanyl group - 427.24±46.86 mins, magnesium group- 365.00±45.99 mins which is statistically significant ('p' value 0.000). Rajesh vasure et al., study the time taken for first request of analgesia in group F (fentanyl 25 mcg) was 238 mins and in group M ($MgSO_4$ 50 mg) was 164 mins. In Beigom et al study time for the first request of analgesia with fentanyl -699 mins compared with $MgSO_4$ (50 mg)-318 mins. In Sarika Katiyar, Chhavi Dwivedi et al. study the time taken for first request of analgesia with fentanyl was 374 mins and $mgso_4$ 100 mg was 328 mins.

It is observed that magnesium failed to prolong the time to first analgesic requirement possible cause is vasodilatory action of $MgSO_4$ which vasodilates tissues around injection site, will eventually accelerates systemic uptake of local anesthetics and also it activates cytochrome p 450 increase bupivacaine hydroxylation and rapid elimination of bupivacaine. The dose requirement of rescue analgesic (diclofenac sodium) in group F was 82.5±6 mg when compared to group M - 165 ±22.5 mg the difference is statistically significant. The findings in our study reinforce the role of magnesium sulfate, an NMDA antagonist, as an effective spinal adjuvant to prevent induction of central sensitization and prolongs duration of analgesia and is an effective alternative to opioids.

Limitations

1. Single doses of drugs have been studied.
2. Plain bupivacaine has not been used in the study.
3. Plasma concentration in specific reference to $MgSO_4$ has not been measured.
4. Other surgeries can be included only infraumbilical surgeries are included.
5. Comparison of $MgSO_4$ and fentanyl can be done in other regional techniques.
6. Sample size is small, it cannot be concluded the results of present study are definitive.
7. More studies are required to conclude results.

Further recommendations

1. There is scope for further studies related to this topic.
2. Different doses of magnesium can be compared and studied.
3. Continuous intrathecal infusion of magnesium can be studied.
4. Synergism of combination of magnesium with other drugs to be evaluated.
5. Use of intrathecal magnesium along with iv or by wound infiltration can be done to study effect of blocking both peripheral and central sensitization, to evaluate its optimal role in reducing postoperative analgesic requirements.

Conclusion

Fentanyl 25 µg and $MgSO_4$ 100 mg as adjuvants to 0.5% heavy bupivacaine prolongs duration of spinal anaesthesia. Fentanyl has faster onset and better quality of analgesia in terms of patient satisfaction its advantages are limited by side effects, magnesium sulphate provides excellent quality of postoperative analgesia and no side effects and is an attractive alternate non-opioid intrathecal adjuvant.

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