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Magnesium Sulphate as an Effective Adjuvant for Postoperative Pain Management in Lower Limb Orthopaedic Surgeries

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Abstract: ***Objective: To observe the total analgesic requirement in the first 24 hrs of the postoperative period, if there is any prolongation of the time to rescue analgesia and incidence of complications in patients given Magnesium sulphate and the control group. Methods: The study comprised 50 patients undergoing lower limb orthopaedic surgery who were ASAGrade I & II and were between the age of 20 and 65. After receiving spinal anaesthesia, 25 of these patients (Group A) got Magnesium Sulphate at a dose of 50 mg/kg in 100 ml bottles of normal saline, while the other 25 patients (Group B) received only NS (Group B). It was recorded when the first dose of analgesia was needed. Patients were watched for signs of sedation, hypotension, shivering, nausea, vomiting and pruritus. The total amount of analgesics needed in the first 24 hours following the operation was noted. Results: In Group A and Group B, the mean ± SD of the time to rescue analgesia was 444± 130 minutes and 287± 55 minutes, respectively. The total analgesic requirement of Group A was significantly less as compared to Group B in the first 24 hours of the surgery. Incidence of complications were not significantly higher in the study group. Conclusion: We come to the conclusion that patients receiving spinal anaesthesia for lower limb orthopaedic procedures can safely receive IV magnesium sulphate in a bolus dose of 50 mg/kg to reduce initial postoperative pain with a minimal incidence of complications.***

Keywords: Magnesium Sulphate, Postoperative Pain Management, Lower Limb Orthopaedic Surgeries, Spinal Anaesthesia, Analgesic Requirement

Main points

- The mean time to rescue analgesia differed statistically significantly between groups A (cases) and B. (control).
- Group A needed fewer analgesics for 24 hours than group B did.
- There was no statistically significant difference between the two groups in the incidence of complications.

1. Introduction

The International Association for the Study of Pain defines pain as "an uncomfortable, sensory, and emotional experience related to actual or potential tissue damage or explained in terms of such damage. " [1] It is common to undertreat postoperative pain that results from inflammation brought on by tissue trauma or direct nerve injury. After surgery, it's critical to maintain good pain management to avoid complications like tachycardia, hypertension, immobility, deep venous thrombosis, and slow wound healing. [2] Starting physiotherapy and ambulation as soon as possible after surgery promotes quick healing and patient satisfaction. Adequate postoperative pain management is crucial for both the recovery from surgery and the avoidance of chronic postsurgical pain. [3]As a result, an essential part of postoperative healing is appropriately controlling postoperative pain. [4] This is because adequate pain control reduces perioperative morbidity by effectively blunting autonomic, somatic, and endocrine reactions.

Orthopaedic surgeries including total knee replacement, lower limb fractures, and arthroscopic ligament repairs result in acute postoperative pain that requires proper management to reduce complications and speed healing. By addressing acute pain head - on, central sensitization can be prevented.

Use of opioids, local anaesthetics, N - methyl - D - aspartate (NMDA) antagonists, alpha - 2 agonists, epidural analgesia, and continuous regional anaesthesia are some of the different methods used to alleviate postoperative pain. However, significant side effects from epidural anaesthesia include meningitis, epidural hematomas, and inadvertent dura punctures. It can be difficult to administer pharmacological thromboprophylaxis postoperatively when an epidural catheter is still in place. Administration of regional analgesia needs peripheral nerve stimulator and ultrasonography which is not available in every hospital setup.

Opioids are currently among the most popular and effective analgesics for the management of moderate to severe pain due to their potency and rapid onset of action. Opioid use has drawbacks due to the wide range of potential side effects, including urinary retention, pruritus, respiratory depression, changes in gastrointestinal motility that can cause constipation or diarrhoea, depression of the central nervous system, nausea or vomiting. The use of PCA pumps to administer opioids is linked to opioid addiction and dependency. [5 - 9]

Drugs classified as adjuvants are those that may help with pain management, but they are not often classified as

analgesics. Ketamine, pregabalin, gabapentin, intravenous lidocaine, 2 - adrenoceptor agonists like clonidine and dexmedetomidine, and magnesium sulphate are a few examples of these adjuvant analgesics. [2]

The magnesium ion is the fourth most common cation in humans [10] and the second most common intracellular cation, after potassium and sodium. Magnesium is accessible in two different forms: magnesium chloride and magnesium sulphate. Most research laboratories use magnesium chloride. The established uses of magnesium sulphate in our institution outside of the operating room include the prevention of seizures in preeclampsia, the treatment of dysrhythmias, and the management of hypomagnesemia. Magnesium sulphate has recently been suggested for use as an efficient analgesic adjuvant for postoperative pain in the field of anaesthesia. [11] Its analgesic effect appears to be related to the control of calcium entry into cells [12] or antagonistic activity on central nervous system N - methyl - D - aspartate (NMDA) receptors. [13, 14] Magnesium sulphate reduces the noxious stimulus - induced somatic, autonomic, and endocrine responses. Magnesium is also recognised to have anti - inflammatory properties [15], which can lessen pain sensitivity in both the central and peripheral nervous systems. [16]

Additionally, postoperative shivering is reported to be less common when magnesium sulphate is used. [17, 18] Shivering is thought to enhance catecholamine release, lactic acidosis risk, hypoxemia, and oxygen demand. [19] Additionally, magnesium sulphate may lessen the likelihood of nausea and vomiting. [20]Magnesium sulphate directly inhibits the smooth muscle of the heart and the blood vessels. It directly inhibits the release of catecholamines from the adrenal medulla and peripheral adrenergic terminals as well as their receptors. As a result, lower cardiac output and vascular tone lead to hypotension and decreased pulmonary vascular resistance. [21, 22] In some ways, it has a sedative effect.

In this trial, patients were observed as they received a bolus dose of 50 mg/kg of magnesium sulphate intravenously in 100 ml of normal saline over the course of 15 minutes to decrease postoperative pain following spinal anaesthesia for lower limb orthopaedic procedures. The time at which patient complaints of pain postoperatively was noted and the total analgesic requirement in 24 hours were noted. The incidence of complications like hypotension, sedation, shivering, pruritus, nausea and vomiting were noted in these patients. Magnesium Sulphate infusion is expected to decrease analgesic requirement in the first 24 hrs and also decrease incidence of shivering, nausea and vomiting. The incidence of complications like hypotension and sedation is expected to be low. An observational study was done on 25 patients who are randomly selected to receive Magnesium Sulphate. These observations were compared with those of 25 patients who did not receive magnesium sulphate. The decision to use Magnesium Sulphate or not wasaccording to randomisation using a closed envelope method bya consultant anaesthesiologist not involved with the observations. The observer was totally blinded to this decision and received this information after the full data was collected to formulate the conclusion. This study was completed over a period of 7 months.

2. Material and Methods

Institutional ethics committee approval was taken after a review meeting.

Sampling Technique: Simple Random Sampling Method using a closed envelope.

Study Design: Observational Study with control group for comparison.

Study Population: This study includes ASA I & II patients in the age group of 20 to 65 years undergoing lower limb orthopaedic surgeries under spinal anaesthesia.

Sample Size
Sample size was calculated using the effect sizes from the previously published study (Revi N. et al. international journal of basic and clinical pharmacology 2003) and with the help of following formula:

$$n\ (Per\ Group) = 2[\frac{\left(Z_{\frac{\alpha}{2}} + Z_{\beta}\right)\sigma}{\Delta}]^2$$

where n = Sample size (per group).
$Z\alpha_{/2}$ = (1.96) for 95% confidence (i.e. = 0.05). = 1.96 [5% level of significance]
$Z\beta$ = Cut-off value for Power (1 - β). = 0.8416 [80% power]
Δ = Mean difference to be detected (minimum difference) = 60 min on average for the need of first rescue analgesia.
Δ / = Effect size in SD units. = 0.790.

[Effect size measures the size of difference between two groups and is an indicator of clinical importance of the result in terms of standard deviation units. Effect size of 0.790 means the group means are expected to differ by 0.790 standard deviations as per the literature evidence (which falls in moderate to high range of effect size). The probability of accepting Null hypothesis (P - value) goes down as the size of the effect goes up and as the size of the sample goes up. In other words the inter - group difference of more than 0.790 standard deviations will be treated as clinically significant, even if the results are not statistically significant.]

Sample size according to this formula is 25.15 ≅ 25 (Minimum Per Group) i. e Total 50 (Minimum).

Statistical Data Analysis:
The data on categorical variables is shown as n (% of cases) and the data on continuous variables is presented as mean and standard deviation (SD) across two study groups. The inter - group statistical comparison of distribution of categorical variables is tested using Chi – Square test or Fisher's exact probability test for 2 x 2 contingency table with cell frequency less than 5. The inter - group statistical comparison of means of continuous variables is done using independent sample t test. The underlying normality assumption was tested before subjecting the study variables to t test. All results are shown in tabular as well as graphical format to visualize the statistically significant difference more clearly. In the entire study, the p - values less than 0.05

are considered to be statistically significant. All the hypotheses were formulated using two tailed alternatives against each null hypothesis (hypothesis of no difference). Statistical Package for Social Sciences (SPSS ver 22.0, IBM Corporation, USA) for MS Windows is used to statistically evaluate all of the data.

Inclusion Criteria:

1) Patients between the age group of 20 and 65 years who are ASA Grade I & II
2) Orthopaedic surgeries done under spinal anaesthesia alone with 0.5 % hyperbaric Bupivacaine injected intrathecally without any adjuvant.

Exclusion Criteria:

1) Patients with cardiovascular, hepatic or renal dysfunction.
2) Patient having a known allergy to Magnesium Sulphate.
3) All patients who are on calcium channel blockers.
4) Patients in which spinal anaesthesia is contraindicated.

Investigations:

As per the protocol of our hospital the investigations mentioned below were done on the day prior to surgery:

1) Hemogram
2) Urine routine and microscopy
3) Blood creatinine and urea levels
4) Prothrombin time and International normalized ratio
5) Liver function tests

3. Methodology

Following a thorough explanation of the trial, all patients gave signed informed consent. All patients underwent a thorough physical examination, a complete history taking, and standard investigations. In accordance with the typical NPO protocols, the patients were kept fasting. Pre - induction parameters of BP, pulse and SpO2 were noted. Spinal anaesthesia was injected into the L3 - L4 or L4 - L5 interspace while the patient was sitting. After puncturing the dura with a 26 G Quincke's needle, hyperbaric 0.5% Bupivacaine solution was injected intrathecally. Bupivacaine dosage was determined by height, with values being as follows: 155 cm = 12 mg, 155 - 170 cm = 13 mg, 170 - 180 cm = 14 mg, and 180 cm > = 15 mg. Time at which spinal anaesthesia was given was noted. T100 ml normal saline bottles were given IV over a period of 15 minutes by the guide. Some had Magnesium Sulphate in the dose of 50 mg/kg. The observer was unaware of the contents. After the observational study was finished and the outcomes were compared, the code's solution was disclosed.

If the mean arterial pressure decreased 20% from baseline or the systolic blood pressure dropped to less than 90 mm Hg, ephedrine 6 mg was injected intravenously. If heart rate dropped to less than 45 beats per minute, 0.6 mg of atropine was injected intravenously. It was documented if the patient ever had hypotension or sedation.

Incidence of nausea, vomiting, shivering and pruritus in the postoperative period was recorded. Time at which patient started moving his legs and time at which patient first complained of pain (VAS score >3) [Figure 6]was noted. Rescue analgesics given in the first 6 hours of the surgery were noted. Patients were followed up for 24 hrs in the ward for the total analgesic requirement.

Assessment Protocol:

- T1: Time at which spinal anaesthesia was given.
- T2: Time when the patient started moving his legs (motor action of spinal anaesthesia wears off)
- T3: Time at which patient complained of pain and VAS score > 3
- T2 – T1: Time of duration of action of spinal anaesthesia.
- T3 – T1: Time to rescue analgesia
- 24 hours analgesic requirement (All the analgesics given to the patient in 24 hrs were noted)

Rescue analgesia was given with I. V Paracetamol 1gm alone or along with I. V Tramadol 50mg I. V in 100 ml normal saline if the patient had shivering. Any incidence of shivering, nausea and vomiting were noted. Total analgesics required at the end of 24 hours were noted.

4. Results

In our analysis, there was no statistically significant difference between group A (cases) and group B in terms of age, sex, BMI, comorbidities, ASA grade, or the type of surgery.

The mean total dose of different analgesics needed in 24 hours in groups A (case) and B (control) differed statistically significantly. With the exception of TKR, the 24hours analgesic requirement in group A (case) is lower than group B (control) in a variety of age groups and types of surgery. This difference is statistically significant (P - value < 0.05 for all). [Table & Figure 1]

The difference between group A (cases) and group B's mean time to rescue analgesia was statistically significant. Comparing groupA (case) to group B (control), the mean time to rescue analgesia [T3 - T1] is longer in group A (case) [444±130] than in group B [287± 55]. This was consistently seen across a range of age groups and surgical specialties. There is a statistically significant difference here. (P - value < 0.05 for all). [Table & Figure 2]

In the first six hours, group A (case) requires less rescue analgesia than group B (control), and this difference is statistically significant. (P - value < 0.05) In the first six hours following surgery, 36% of patients in group A (case) and 88% of patients in group B (control) needed analgesics. [Table&Figure 3]

The mean spinal anaesthesia action time [T2 - T1] in group A (case) [245±22] is longer than in group B (control) [209±23], which is statistically significant. With the exception of TKR, the mean duration of action of spinal anaesthesia in Group A (Case) is longer than in Group B (Control) across a range of age groups and surgical procedures, and the difference is statistically significant. (P - value<0.05 for all). [Table & Figure 4]

20% (n=5) of the patients in group A (case) and 20% (n=5) of the patients in group B experienced episodes of hypotension, in comparison, when it comes to complications. Sedation was seen in 16% (n=4) of patients in group A (case) and 4% (n=1) of patients in group B. Shivering episodes were experienced by 16% (n=4) of patients in group A (case) and 16% (n=4) of patients in group B.12% (n=3) of patients in group B and 4% (n=1) of patients in group A (case) experienced nausea episodes, respectively. In group A (case), 4% (n=1) of patients experienced vomiting, and group B (control), 4% (n=1). [Table & figure 5]

In both groups, none of the patients developed pruritus. The incidence of complications like hypotension, sedation, shivering, nausea, vomiting, and pruritus was the same in both groups and did not differ statistically. (P - value>0.05 for all)

5. Discussion

Antinociceptive action of Magnesium sulphate is mediated by antagonism of NMDA receptors and decreased calcium mediated neurotransmitter release. The central sensitization of pain has been shown to decrease and the duration of the sensory block to lengthen when NMDA receptors are blocked. Magnesium inhibits the release of acetylcholine from motor nerve terminals and directly lowers the excitability of muscle fibre membranes, both of which contribute to a motor blockade.

In our study, patients who underwent spinal anaesthesia for lower limb orthopaedic procedures were assessed for the analgesic efficacy of intravenous magnesium sulphate.25 patients which received IV Magnesium Sulphate in the dose of 50 mg/kg in 100 ml Normal Saline, Group A (case) were compared to 25 patients which received 100 ml Normal saline, Group B (control) for requirement of analgesic drugs in 24 hours of postoperative period. The time to rescue analgesia was also observed. Comparisons between the two groups were made for problems such hypotension, sedation, nausea, vomiting, shivering, and pruritus.

Analgesic Effect

In Group A, the time to rescue analgesia was extended. In the first six hours following surgery, only 36% of patients in Group A (the case) required analgesics, compared to 88% of patients in Group B (the control), who required analgesics in the same time period. It was statistically significant that there was a difference in the need for analgesics.

Group A (the case) needed fewer analgesics than group B (the control) in the first 24 hours following surgery, and the difference was statistically significant. The dosages of injection Diclofenac, injectable Paracetamol, and opioids needed by Group B were higher. Tramadol, Diclofenac, and Paracetamol injections successfully treated the patients in Group A (case). When analgesic requirement was compared in various types of orthopaedic surgeries, our study found that the 24 hours analgesic requirement for lower limb fracture surgeries and arthroscopic ligament repair was less in group A (case) as compared to group B (control). This difference was statistically significant. There was no statistically significant difference in the 24 hours analgesic requirement for Total Knee Arthroplasty in Group A (case) and Group B (control) but clinical significance needs to be evaluated further.

In our study we observed that the time for spinal anaesthesia to wear off was also increased significantly in Group A though it was not included in our primary objective.

Complications

Complications such hypotension, sedation, nausea, vomiting, shivering, and pruritus were looked for in both groups of patients.

All groups had an identical incidence of hypotension.20% of patients in group A and 20% of patients in group B experienced episodes of hypotension, which were successfully treated with injection ephedrine 6 mg IV. Magnesium sulphate didn't make hypotension more common in our study.

Sedation occurred more frequently in Group A (the case) of our study than in Group B (the control), but this difference was not statistically significant.

Cases in Group A (cases) felt less nauseous than those in Group B. (control). This difference was clinically important even if it was not statistically significant.

Vomiting was prevalent in both groups on an equal level.

In our study, post - operative shivering was reported by 16% of patients in Group A and 16% of patients in Group B. They were kept under control for 15 minutes by an injection of tramadol 50 mg IV administered in 100 ml of normal saline. Both groups experienced shivering on a comparable level. Magnesium sulphate did not significantly improve shivering in our trial.
Both groups did not exhibit pruritus.

Limitations

The limitations of our study were as follows –

1) Inability to measure serum magnesium levels
2) Inability to use Patient control analgesia (PCA) for postoperative analgesia
3) Prolonged follow up of patients after the first 24 hrs of postoperative period was not done.
4) Comparison of Magnesium with other agents was not studied.

6. Conclusion

Our research showed that the overall amount of analgesics needed in the first 24 hours following surgery can be decreased by administering magnesium sulphate in a bolus dose of 50 mg/kg in 100 ml normal saline during a 15 - minute period. This dose is efficient in extending the time to rescue analgesia in patients undergoing lower limb orthopaedic procedures and greatly reducing the analgesic required in the first six hours of surgery. Although sedation was observed in a few of our study group individuals, it was not statistically significant. Magnesium sulphate did not appear to reduce postoperative shivering in our study, which

occurred in both the study and control groups. In both groups, the prevalence of complications like hypotension was comparable. We come to the conclusion that patients receiving spinal anaesthesia for lower limb orthopaedic procedures benefit from a bolus dosage of 50 mg/kg IV magnesium sulphate with minimal incidence of complications. This mode of attenuating postoperative pain can be effectively and safely used in low resource settings.

7. Recommendation

I would like to recommend the use of Magnesium sulphate in a dose of 50 mg/kg as an intravenous adjuvant to spinal anaesthesia. It decreases requirement of analgesics including opioids in the postoperative period especially in lower limb fracture surgeries and arthroscopic ligament repair. More studies need to be done with larger numbers to evaluate this further. As an intravenous adjunct to spinal anaesthesia, magnesium sulphate is inexpensive, conveniently accessible, and generally safe with minimal side effects.

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Tables

Table 1: Inter - group comparison of total dose of analgesics required in 24 - hrs in various surgery groups.

Surgery Group	Total analgesics required in 24 - hrs (Dose)	Group A [Case] (n=25)		Group B [Control] (n=25)		P - value
		Mean	**SD**	**Mean**	**SD**	
Fracture	Paracetamol (gm) (n=7/n=11)	1.57	0.79	1.91	0.30	0.212^{NS}
	Diclofenac (mg) (n=6/n=6)	100.0	38.7	150.0	0.00	0.010^{**}
	Tramadol (mg) (n=4/n=7)	50.0	0.0	78.6	26.7	0.066^{NS}
	Pentazocine (mg)	- -	- -	- -	- -	- -
ALR	Paracetamol (gm) (n=9/n=8)	1.22	0.44	1.62	0.52	0.104^{NS}
	Diclofenac (mg) (n=5/n=5)	90.0	33.5	135.0	33.5	0.067^{NS}
	Tramadol (mg) (n=4/n=2)	50.0	0.0	100.0	0.0	0.188^{NS}
	Pentazocine (mg) (n=0/n=1)	- -	- -	30.0	- -	- -
TKR	Paracetamol (gm) (n=3/n=3)	1.67	0.58	1.67	0.58	0.999^{NS}
	Diclofenac (mg) (n=1/n=1)	75.0	- -	150.0	- -	- -
	Tramadol (mg) (n=2/n=2)	100.0	0.0	100.0	0.0	0.999^{NS}
	Pentazocine (mg) (n=0/n=1)	- -	- -	30.0	- -	- -
Values are mean and SD, P - value by independent sample t test. P - value<0.05 is considered to be statistically significant. **P - value<0.01, NS – Statistically non - significant.						

There is a statistically significant difference between the mean of total dose of analgesics required in 24 hrs in various surgery groups in Group A and Group B except for TKR (P - value<0.05 for all).

Table 2: Inter - group comparison of mean time to rescue analgesia.

Time (Mins)	Group A [Case] (n=25)		Group B [Control] (n=25)		P - value
	Mean	SD	Mean	SD	
T3 – T1 [Time to rescue analgesia]	444.0	130.0	287.0	55.0	0.001^{***}
Values are mean and SD, P - value by independent sample t test. P - value<0.05 is considered to be statistically significant. ***P - value<0.001.					

The mean ± SD of time to rescue analgesia [T3 - T1] in Group A (Case) and Group B (Control) was 444 ± 130 Mins and 287 ± 55 Mins respectively. There is a statistically significant difference in mean time to rescue analgesia [T3 - T1] in Group A (case) as compared to group B (control) (P - value<0.05).

Table 3: Inter - group distribution of requirement of rescue analgesia in first 6 - hrs.

Requirement of rescue analgesia in first 6 - hrs	Group A [Case] (n=25)		Group B [Control] (n=25)		P - value
	n	**%**	**n**	**%**	
Not required	16	64.0	3	12.0	0.001^{***}
Required	9	36.0	22	88.0	
Total	**25**	**100.0**	**25**	**100.0**	
Values are n (% of cases), P - value by Chi - Square test. P - value<0.05 is considered to be statistically significant. ***P - value<0.001.					

The requirement of rescue analgesia in first 6 - hrs is significantly higher in Group B (Control) compared to Group A (Case) and the difference is statistically significant. (P - value<0.05)

Table 4: Inter - group comparison of mean duration of action of spinal anaesthesia [T2 - T1] in various types of surgeries

Time (Mins)	Surgery group	Group A [Case] (n=25)		Group B [Control] (n=25)		P - value
		Mean	SD	Mean	SD	
T2 – T1 [Time of duration of action of Spinal anesthesia]	Fracture	246	22	214	25	0.003^{**}
	ALR	248	21	202	21	0.001^{***}
	TKR	230	23	210	24	0.323^{NS}
Values are mean and SD, P - value by independent sample t test. P - value<0.05 is considered to be statistically significant. *P - value<0.05, **P - value<0.01, ***P - value<0.001, NS – Statistically non - significant.						

There is a statistically significant difference in meanduration of action of spinal anaesthesia [T2 - T1] in Group A [Case] compared to Group B [Control] in all types of surgeries except for TKR (P - value<0.05 for all).

Table 5: Inter - group distribution of incidence of complications.

Complications	Group A [Case] (n=25)		Group B [Control] (n=25)		P - value
	n	**%**	**n**	**%**	
Hypotension	5	20.0	5	20.0	0.999^{NS}
Sedation	4	16.0	1	4.0	0.349^{NS}
Shivering	4	16.0	4	16.0	0.999^{NS}
Nausea	1	4.0	3	12.0	0.609^{NS}
Vomiting	1	4.0	1	4.0	0.999^{NS}
Pruritus	0	0.0	0	0.0	0.999^{NS}
Values are n (% of cases), P - value by Chi - Square test. P - value<0.05 is considered to be statistically significant. NS – Statistically non - significant.					

There is no statistically significant difference between the complications such as hypotension, sedation, shivering, nausea, vomiting and pruritus studied in Group A and Group B (P - value>0.05 for all).

Abbreviations:

- ASA: American Society of Anaesthesiologists
- BMI: Body Mass Index
- GABA: Gamma Amino Butyric Acid
- NMDA: N Methyl D Aspartate
- Min: Minute
- Hrs: Hours
- PCA: Patient Controlled Analgesia
- VAS: Visual Analogue Scale
- IV: Intravenous
- TKR: Total Knee Arthroplasty

Figure Legends:

Figure 1	Inter - group comparison of mean of total dose of analgesics required in 24 - hrs in various surgery groups.
Figure 2	Inter - group comparison of mean time to rescue analgesia
Figure 3	Inter - group distribution of incidence of requirement of rescue analgesia in first 6 - hrs.
Figure 4	Inter - group comparison of mean duration of action of spinal anaesthesia [T2 - T1] in various types of surgeries
Figure 5	Inter - group distribution of incidence of complications.
Figure 6	VISUAL ANALOGUE SCALE