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VARIATIONS IN THE CLINICAL AND ANAESTHETIC PARAMETERS DURING ADMINISTRATION OF ROPIVACAINE AND FENTANYL AS LUMBOSACRAL ANAESTHESIA IN GOATS

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ABSTRACT

The aim of study was to assess the quality of analgesia and record the alteration in clinico-anesthetic indices following epidural administration of ropivacaine alone and its combination with fentanyl. A total of 10 clinically healthy goats of 1-3 years aged and weighing between 10-15 kg were used for the present experiment. All the animals were randomly divided into two groups of five animals each. Ropivacaine (0.75%) @ 1 mg/kg BW was administered epidurally at the lumbosacral space in group 1 whereas, the animals of group 2 were given fentanyl @ 2 µg/kg BW in combination with ropivacaine hydrochloride (1 mg/kg BW). Rectal temperature, respiration rate and heart rate showed non- significant (P>0.05) variations in both the groups. Duration of analgesia in the different parts of hindquarter was longer in group II as compared to group I. Analgesia, motor incoordination and sedation depicted greater degree in group II. The results suggest that the ropivacaine alone or in combination with fentanyl produced effective analgesia (sensory and motor) of different parts of the hindquarters with little effect on physiology. However, the combination groups manifested higher degree of analgesia, motor incoordination and sedation.

Key words: Analgesia, clinico- anaesthetic variations, fentanyl, goats, ropivacaine.

INTRODUCTION

Ropivacaine is a long acting amide local anesthetic agent and first produced as a pure enantiomer. Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibre, resulting in a relatively reduced motor blockade. Thus, ropivacaine has a greater degree of motor sensory differentiation, which could be useful when motor blockade is undesirable (Kuthiala and Choudhary, 2011). Ropivacaine has been used in animals as epidural anaesthesia for achieving hindquarter analgesia in goats (Khajuria *et al*., 2014; Singh *et al*., 2015) and in dogs (Khodwe *et al.* (2013). Epidural opioids have been used extensively to provide analgesia in companion animals (Pascoe, 2000; Wagner, 2002) and horses (Robinson and Natalini, 2002).

Fentanyl citrate is a potent opioid agonist. The principle actions of therapeutic value are analgesia & sedation. Opioids like fentanyl have been used traditionally as an adjunct for epidural administration in combination with lower dose of local anaesthetic to achieve the desired anaesthetic effect (Wang *et al.*, 1993). Fentanyl as an adjuvant with ropivacaine may improve the quality of spinal block with ropivacaine (Doctor *et al*., 2013; Jagtap *et al.* 2014) in humans. As per literature cited, no work has yet been reported in animals using ropivacaine in combination with fentanyl.

Hence the present report is described to be the first one to find out the quality of analgesia and to record the alteration in clinico-anesthetic indices following epidural administration of ropivacaine and its combination with fentanyl in goats.

MATERIALS AND METHODS

The present study was conducted on 10 clinically healthy female black Bengal goats of 1-3 years of age and weighing between 10-15 kg. They were divided into two groups with 5 goats in each group. Each goat was selected to one treatment of epidural administration. The work was approved by Institutional Animal Ethical Committee (IAEC), letter no. 143 dated: 23.06.15.

Ropivacaine 0.75% (Ropin – NEON Pharmaceutical Laboratories Limited, 28 Mahal Ind. Est., M Caves Rd., (East), Mumbai -400093) @ 1 mg/kg BW was epidurally administered in the lumbosacral space in group 1 whereas, the animals of group 2 were given fentanyl citrate (Trofentanyl – Troikaa Pharmaceuticals Ltd.Thol-382 728, Gujrat, India) @ 2 µg/kg BW in combination with ropivacaine hydrochloride (1 mg/kg BW). A total volume of 3 ml should be kept constant by addition of distilled water in all the goats. Baseline data of different parameters were obtained before administration of analgesic agents.

To accomplish epidural block, an 18-gauge 3.5 cm hypodermic needle was inserted percutaneous at the prepared site into the lumbosacral epidural space to inject analgesic agent. Following epidural administration of analgesic agents different clinico-physiological and anaesthetic parameters were carried out at the time intervals of 0, 15, 30, 60, 90, 120 and 240 minutes, respectively, after epidural administration of analgesic agents.

Clinico-physiological observations: Rectal temperature (°F), heart rate (beats/ min) and respiration rate (breaths /min) were recorded before and at different time intervals as mentioned above after administration of different analgesic agents.

Anaesthetic observations

Analgesia was scored using a 0-3 numerical rating scale to pin-prick response as:
0 - No analgesia (strong reaction to pin prick)
1 - Mild (weak response to pin prick)
2 - Moderate (occasional response to pin prick)
3 - Excellent (no response to pin prick)

Depth of analgesia and area of desensitization: The presence of analgesia was observed by pin prick at posterior abdomen (caudal to umbilicus), anterior abdomen (cranial to umbilicus up to diaphragm), thigh region, tail, perineum, anal region and pedal reflex (digits of hind limb) at 0 (before injection), and at 15, 30, 60, 90, 120 and 240 min. after the injection of drugs.

Motor in-coordination/ataxia were graded as 0-3 scale:
0 – Walking without staggering
1 – Able to stand and walk with little incoordination
2 – Frequent swaying of the body but animal able to stand and able to walk with extreme incoordination
3 – Unable to stand and assumed recumbency

Sedation was assessed by observing drowsiness and lowering of the head, and scored using a 0-3 numerical rating scale:
0 - Fully alert
1 - Alert but unable to walk
2 - Drowsy and unable to stand
3 - Heavily sedated/asleep

Anaesthetic indices: The anaesthetic indices like onset of analgesia, duration of analgesia, time to recumbency and time to standing were noted in each treated goat on the basis of physical symptoms and reflexes.

Statistical analysis: ANOVA and DMRT were used to compare the means at different intervals with base values as per method described by Snedecor and Cochran (1991). Non-parametric observations were statistically analysed by Krushkal Wallis one-way analysis of variance. The level of significance for non-parametric observations was further tested by selecting Bonferrini test. The level of significance was set at 0.05.

RESULTS

Clinico-physiological observations: The animals of group 2 exhibited significant increase in rectal temperature at120 and 240 mins of epidural administration as compared to the base line values (Table. 1). Contrarily, group1 exhibited non- significant fall in rectal temperature at various intervals of epidural administration. The values recorded in group 2 and l at these intervals were non-significant (P>0.05).

The values of respiratory rate and heart rate recorded in group l and 2 also showed a non-significant decrease at different intervals of observation i.e. from time 0 (before) till 240 min, following administration of epidural anaesthetics (Table. 1). The values recorded at different intervals were nonsignificant among the groups, except the value recorded at 240 min after administration of drug in group 1, which exhibited significantly higher value as compared to the value recorded in group 2.

Analgesia: Ropivacaine and ropivacaine – fentanyl produced complete analgesia of thigh, tail, perineum and anal region up to 120 min of observation (Fig.1-4). However, mild analgesia was observed to persist on these areas only in group 2 as compared to group 1 at 240 min of observation. Mild to moderate analgesia was noticed in upper abdomen (cranial to umbilicus), posterior abdomen (caudal to umbilicus) and pedal reflex (Fig.5-7). Group 2 (ropivacaine – fentanyl) exhibited moderate anal reflex at 15 min post anaesthetic injection which progressed to absent at 90 min., then it returned to moderate and then normal reflex at the intervals of 120 and 240 min, respectively. Pedal reflex was abolished up to 90 min of observation post anaesthetic in both the groups; however the value recorded on 120 min of observation in group l was significantly higher as compared to group 2.

Motor in-coordination: Ataxia was a consistent finding with higher degree at 120 min post anaesthetic in both the groups. Ataxia was scored as a minimum at 240 min post-anaesthesia, but it was remained higher in group 2 as compared to group l (Fig.8).

Sedation: Sedation was recorded in all the animals up to 120 min after epidural injection however a higher degree of sedation was noticed in group 2 as compared to group l (Fig.9).

Anaesthetic indices (onset of analgesia, duration of analgesia, time of standing and time of recumbency): Onset of analgesia was faster in group 1 (5.8±0.66 min) as compared to group 2 (6.2±0.28 min) however, these values did not differ significantly with each other (Table. 2). The recumbency time observed in both the groups

also exhibited similar trends as observed for onset of analgesia but these values were also non-significant (P>0.05). Duration of analgesia was non-significantly higher in group 2 (4.65±0.34 hrs) as compared to group 1 (4.10±0.44 hrs). The Mean±SE values of standing time were recorded to be 4.28±0.39 and 4.81±0.38 hrs in group 1 and 2, respectively. Group 1 and 2 did not differ significantly in terms of duration of standing time..

Untoward effects: Frequent and scanty urination was the consistent finding in both the groups after epidural administration of drugs. Defecation and shivering was not reported in any of the animals during experimental study.

Table. 1. Mean ± SE values of rectal temperature (^{0}F), respiration rate (/min) and heart rate (beats/min) at different intervals in animals of group 1 and 2.

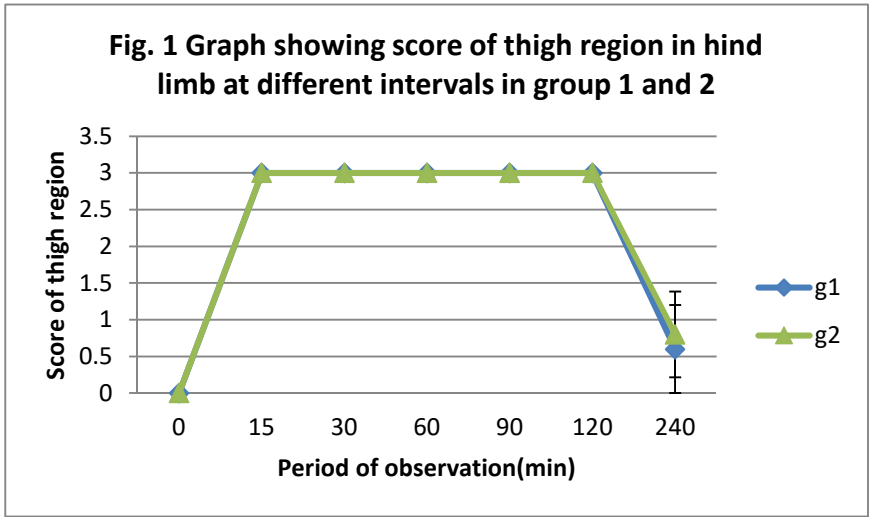
Parameters	Groups	Period of observation (min)						
		0	15	30	60	90	120	240
Rectal temperature	1	102.84 ±0.15	102.72 ±0.29	102.60 ±0.21	102.24 ±39^{A}	102.28 ±0.29	102.32 ±0.28	102.80 ±0.17
	2	101.76 ±0.48^{a}	103.00 ±0.45^{ab}	102.68 ±0.42^{ab}	102.64 ±0.33^{abAB}	102.96 ±0.50^{ab}	103.04 ±0.40^{b}	103.40 ±0.45^{b}
Respiration rate	1	39.60 ±2.04^{B}	36.60 ±2.68^{AB}	32.00 ±2.83^{AB}	32.80 ±3.88^{AB}	30.00 ±1.79	30.20 ±2.62	40.00 ±7.04^{AB}
	2	33.60 ±2.04^{A}	31.60 ±3.4^{A}	29.20 ±2.94^{A}	26.80 ±1.50^{A}	29.60 ±2.04	30.80 ±2.15	29.60 ±2.71^{A}
Heart rate	1	97.60 ±6.27	90.80 ±5.71	90.80 ±7.68	94.80 ±8.93	86.00 ±7.04	86.40 ±5.15	94.80 ±4.89^{AB}
	2	94.40 ±3.50	88.00 ±4.19	85.00 ±4.07	88.00 ±4.56	87.20 ±5.85	84.00 ±6.57	89.00 ±5.74^{A}

Group1: Ropivacaine, Group 2: Ropivacaine + Fentanyl
Value bearing different superscripts in small letter within groups and capital letter among groups differed significantly (P<0.05).

Table. 2. Mean ± SE values of different parameters of anaesthetic indices after epidural administration of drugs in the animals of group 1 and 2.

Parameters of anaesthetic indices	Groups	
	1	2
Onset of analgesia (min)	5.80±0.66	6.20±0.28
Duration of analgesia (hrs)	4.10±0.44	4.65±0.34
Time of standing (hrs)	4.28±0.39	4.81±0.38
Time of recumbency (min)	6.6±1.077	8.4±2.15

Group 1: Ropivacaine, Group 2: Ropivacaine + Fentanyl
Value did not differ significantly among the groups (P>0.05)



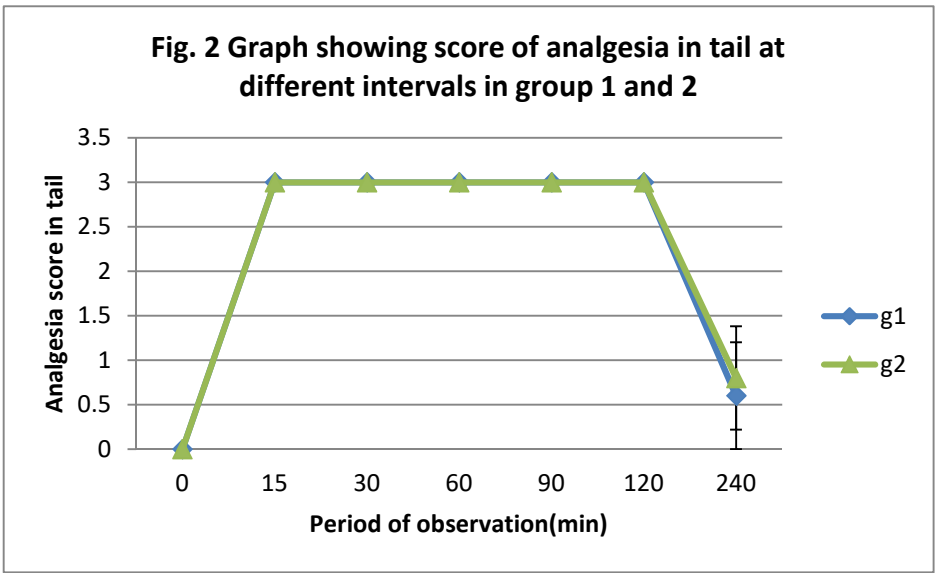


Fig. 2 Graph showing score of analgesia in tail at different intervals in group 1 and 2

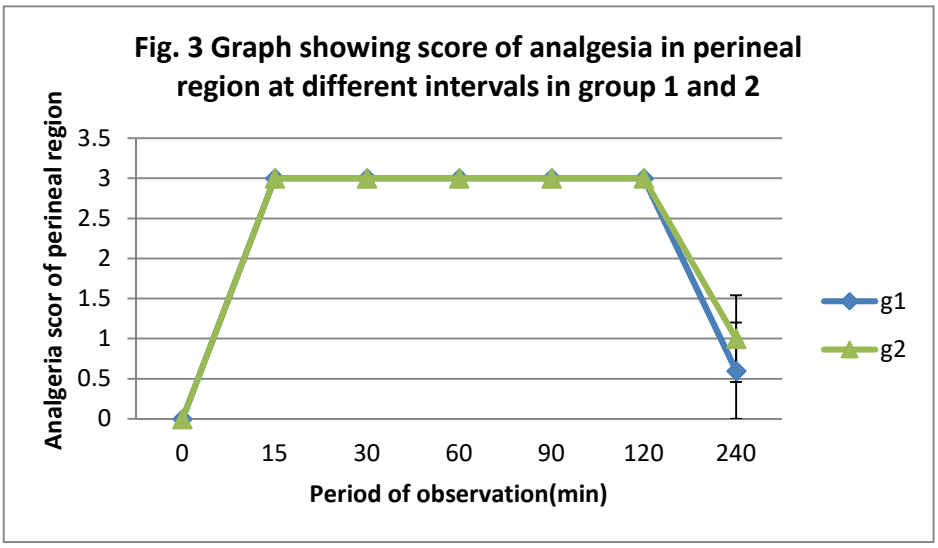


Fig. 3 Graph showing score of analgesia in perineal region at different intervals in group 1 and 2

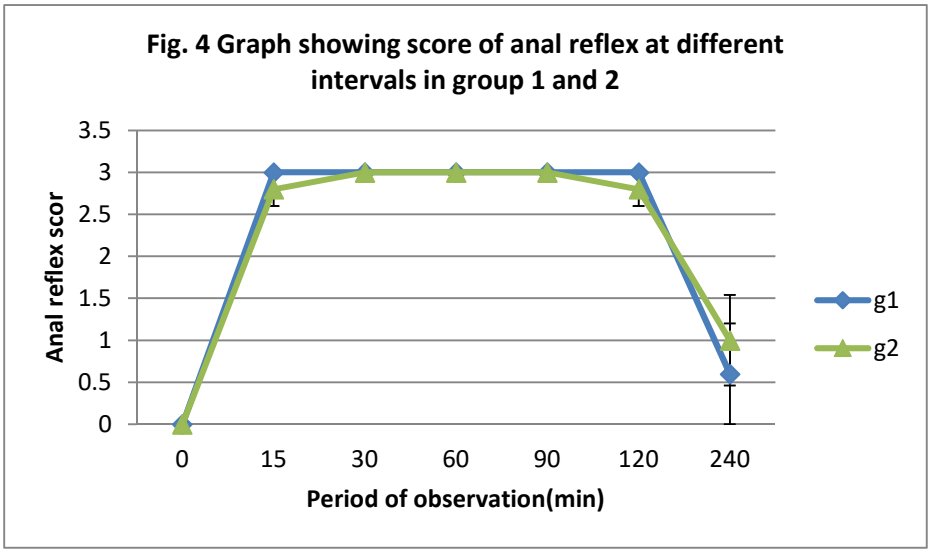


Fig. 4 Graph showing score of anal reflex at different intervals in group 1 and 2

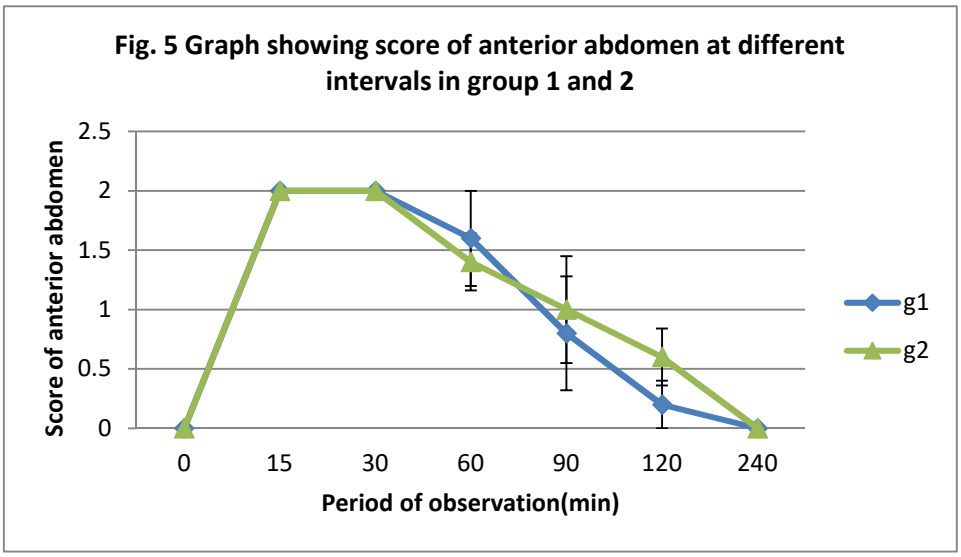


Fig. 5 Graph showing score of anterior abdomen at different intervals in group 1 and 2

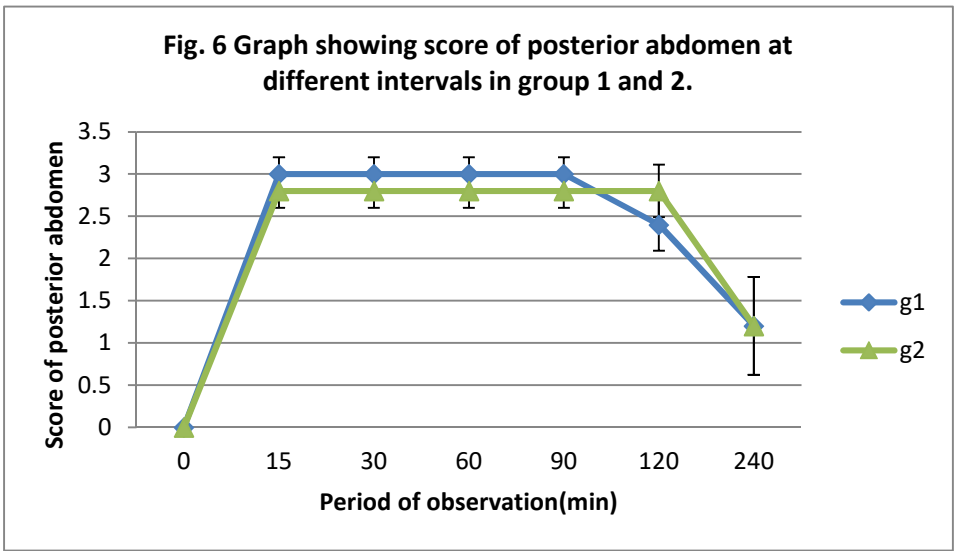


Fig. 6 Graph showing score of posterior abdomen at different intervals in group 1 and 2.

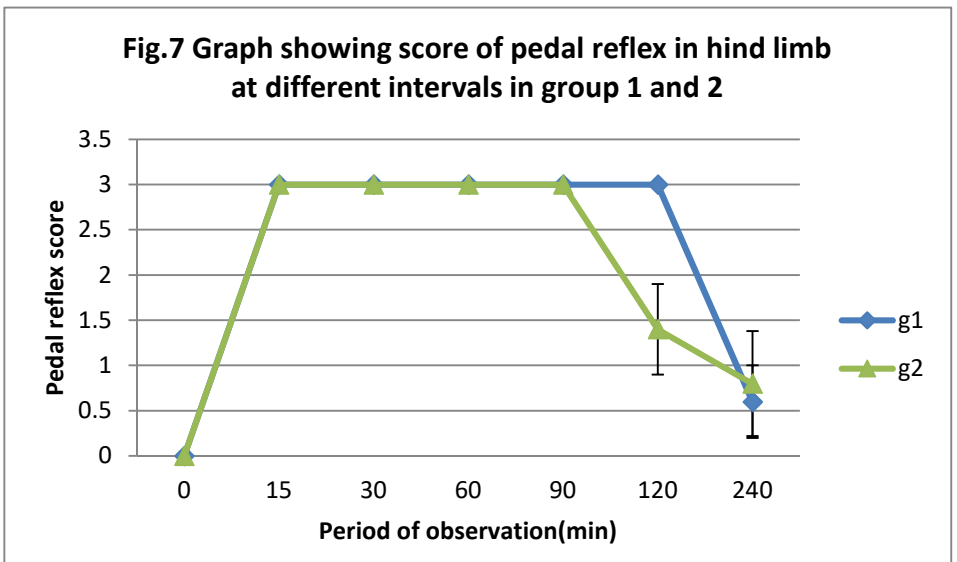
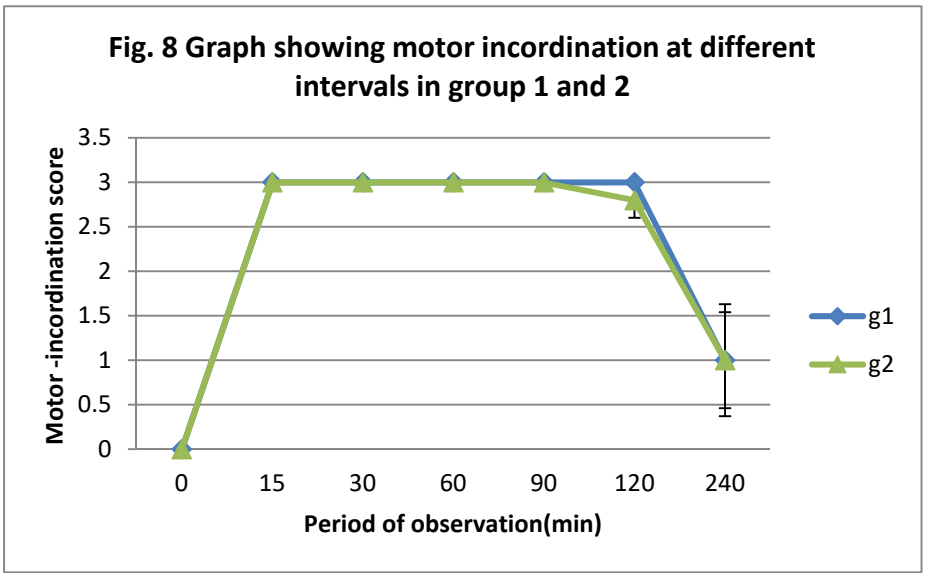
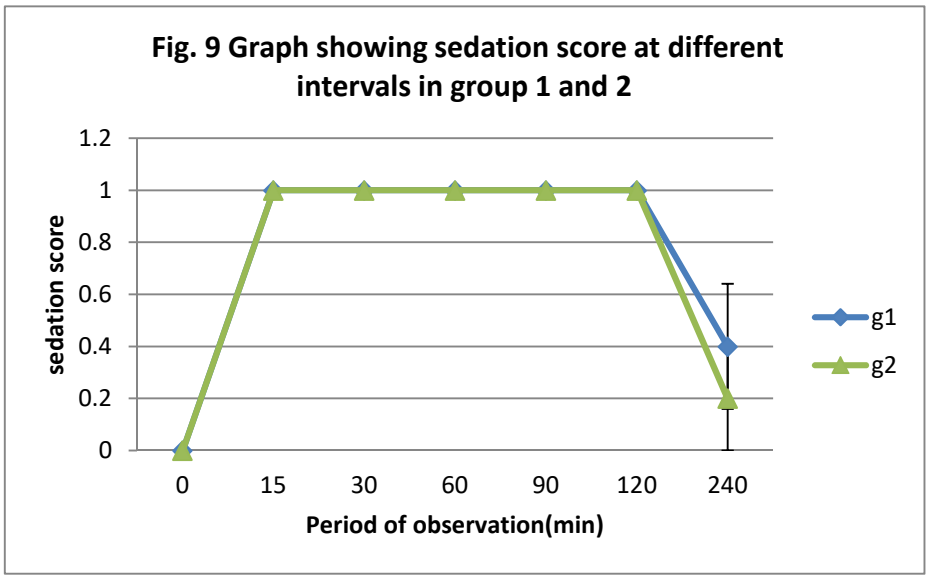


Fig.7 Graph showing score of pedal reflex in hind limb at different intervals in group 1 and 2





DISCUSSION

Hypothermia after epidural administration of local anaesthetic may be due to heat loss resulting from relaxation of thoracic and abdominal skeletal muscles. The reason behind this was again attributed to fall in ambient temperature during course of trial or due to generalized sedation and decreased metabolism (Tanaka *et al.*, 2014). In present study ropivacaine treated group was recorded with non significance alterations in rectal temperature at different intervals after epidural administration, simulated with study conducted in goats (Ahmad and Shukla, 2011) and in buffalo calves (Amarpal *et al.*, 2007) after epidural ropivacaine (0.75%). The increase in rectal temperature in ropivacaine – fentanyl group (group 2) might be explained by the fact that during anaesthesia two goats were excited and struggling which could have resulted in increase in the tonicity of muscle responsible for rise in rectal temperature at some intervals. However, the values remained within normal physiological limits. A non-significant increase was also reported by Khajuria *et al.* (2014) after epidural ropivacaine in goats.

The most direct mechanism that produces respiratory compromise by local anaesthetic probably involves blocking of nerve innervating the muscles of respiration (Blass and Shires, 1986). However, some of earlier reports in goats have indicated that epidural or spinal anaesthesia with local anaesthetic seems to have no significant effect on respiratory system (Habibian *et al*., 2011; Dehkordi *et al*., 2012; Khajuria *et al.*, 2014). Respiratory depression by local anaesthetic alone and in combination with narcotic as observed in the present study is in concurrence with the finding of Skarda and

Muir (1982) in cattle, Kinjavdekar (1998) in goats and Singh *et al.* (2005) in buffalo calves. The κ- opioid agonist are less likely to induce respiratory depression as compared to μ opioid agonist (Pascoe, 2000). The opioids follow slowly the passive circulation of CSF in the spinal subarachnoid space 4 to 6 hour interval to reach the cistern of brain and thus reach the respiratory centre by the ventral pons thus way responsible for respiratory depression.

The heart rate showed a non-significant decrease in ropivacaine and ropivacaine- fentanyl treated groups, which is in agreement with the findings of Amarpal *et al.* (2007). The finding observed in the present study is also in agreement with the findings of Skarda and Muir (2001) and Ganidagli and Others (2004) who observed with no significance change in heart rate after epidural administration of 0.5% of ropivacaine in mare. Contrary to this, Khajuria *et al.* (2014) recorded significantly higher heart rate after epidural administration of ropivacaine @1 mg/kg BW in goats undergoing laparoscopic assisted embryo transfer in goats. In the present study, ropivacaine and fentanyl revealed the mild bradycardia which might be due to direct effect on sinoartrial and atrioventricular conduction causing asystole leading to bradycardia as suggested by Naeine *et al*. (2004). Hypotension may also be developed due to blockage of the sympathetic fibres in thoracic spinal cord due to the use of local anaesthesia (Seyrek-intas *et al.,* 2001).

In the present study, the dose of ropivacaine was same in both the groups, only the combination of fentanyl was combined with ropivacaine. The volume which was administered through epidural route was same. Hence, the reason for cephalic spread due to variability in volume was criticized. Therefore, the analgesic effect found in the different part of body with higher and longer time in group 2 as compared to group1 might be due to synergistic effect of fentanyl in combination with ropivacaine. The synergistic interaction between two drugs might be due to their ability to produce spinal analgesia through different mechanism by acting at different site of action (Hall *et al.,* 2001). Comparatively shorter (360 min) time required for the return of full perineal sensation in cattle following caudal epidural block with ropivacaine reported in recent study (Araujo *et al.,* 2012).The present findings of analgesia with ropivacaine was in support of the present study after epidural ropivacaine produced moderate analgesia for 180 min in goats undergoing laparoscopy assisted embryo transfer (Khajuria *et al.,* 2014). Ropivacaine group also exhibited good analgesia as also observed by Johnson and others (1996). Ropivacaine is less lipophilic (Mc Clellan and Faulds, 2000) and there may be a similar relationship between the volume of ropivacaine administered and its cephalic distribution. Ropivacaine is less likely to penetrate large myelinated motor fibres due to its less solubility in lipids, therefore, it has selective action on the pain transmitting Aβ and C nerves rather than Aβ fibres, which are involved in motor function.

Ataxia was observed in both the groups after administration of epidural agent and there after the animals became recumbent. Contrary to this, Skarda and Muir (2001) observed minimal ataxia in mare with 0.5% ropivacaine injected epidurally. The ataxia and recumbency that coincided with onset of analgesia might be due to diminished blockage of sensory sympathetic and motor fibre by the drug.

Moderate sedation was observed with ropivacaine in goats (Singh *et al.,* 2015). Sedative action in group 2 (ropivacaine- fentanyl) might be explained to have synergistic action and absorption of fentanyl from epidural space systemically. Similar finding has also been reported after epidural administration of morphine, fentanyl, methadone, lignocaine and lignocaine-epinephrine in cattle (Naeine *et al.,* 2004) and ropivacaine in buffalo and cows (Amarpal *et al.,* 2007; Aksoy *et al.,* 2012).

Contrary to present findings, the onset of analgesia was found to be 12.66 ± 1.99 min with ropivacaine in goats (Khajuria *et al.,* 2014). Yayla and Kilic (2010) observed onset of analgesia to be 7.00±1.00 min in hyperbaric ropivacaine in calves. For fentanyl-ropivacaine combination, Al-Ghanem *et al.* (2009) inferred that epidural administration of morphine – fentanyl shorten the onset of analgesia because fentanyl is lipophilic μ receptor agonist opioids causing fast onset and a short duration of action which is also in contrast with present findings. When administered epidurally, it is rapidly absorbed into epidural fat and the systemic circulatory system, resulting in minimum contact time with spinal opioid receptors.

Longer duration of analgesia might be due to synergistic effect of fentanyl along with ropivacaine. Long duration of regional analgesia following epidural use of ropivacaine in various animal species has been reported by several workers (Skarda and Muir, 2001; Amarpal *et al.* 2007; Ahmad and Shukla, 2011; Khajuria *et al.,* 2014). Ropivacaine is longer acting local anaesthetic which is effective when given epidurally over a wide range of concentration (Hall *et al.,* 2001). Ropivacaine without opioids may be used as an alternative to bupivacaine 0.5% with fentanyl, although it did not induce faster onset but provide more prolonged motor block (Christelis *et al.,* 2005). Ropivacaine causes reversible inhibition of Na ion influx and thereby blocks impulse conduction in nerve fibre (Hansen, 2004).This action is potentiated by dose dependent inhibition of potassium channels (Kindler *et al.,* 2003).

Fentanyl showed its effect in substantia gelatinosa that is in dorsal horn of spinal cord blockade is done with inhibition of neuronal excitation in both pre-synaptic and post -synaptic levels. In this way pain

transmission is selectively blocked (Cousins and Mather, 1984). As fentanyl has no effect on sympathetic and motor neurons, it has advantages over local anaesthetics, however when it is used alone, analgesia will not be enough. Due to this reason it was combined with ropivacaine. The efficacy of epidural ropivacaine has been compared with intravenous morphine, epidural bupivacaine, and ropivacaine in combination with fentanyl. Ropivacaine, with or without morphine, was more effective at relieving postoperative pain than intravenous morphine alone (Jayr *et al.,* 1998). Berti *et al.* (2000) reported similar results in terms of pain with epidural use of ropivacaine- fentanyl and bupivacaine-fentanyl. In contrary to this, Doctor *et al.* (2013) reported that ropivacaine- fentanyl combination was found to be better combination as compared to bupivacaine- fentanyl in umbilical surgery in human. Adverse side effects following epidural opioids include respiratory depression, pruritis, nausea, vomition and urinary retention (Chaney, 1995).

It is concluded that ropivacaine alone or in-combination with fentanyl produces effective analgesia (sensory and motor) of different parts of the hindquarters with little effect on physiology. However, Analgesia, motor incoordination and sedation were more marked with ropivacaine and fentanyl combination to permit longer duration of operative procedures involving hindquarter area (posterior to umbilicus).

Author' contribution: Lalita Kumari and A.K. Sharma designed and conducted the work, Laxmi kumari and Chandrakala have been involved in the collection of samples and research materials , whereas, M. P. Sinha and M. K. Gupta critically revised the manuscript.

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