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RESEARCH PAPER

Combination of magnesium sulphate and ropivacaine epidural analgesia for hip arthroplasty in dogs.

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Running head: Epidural magnesium in dogs

Acknowledgements

Authors' contributions

Abstract

Objective The aim of this study was to determine whether lumbosacral epidural administration of magnesium sulphate added to ropivacaine prolongs and improves perioperative analgesia, without adverse effects on motor block duration or hind limb neurological function, in dogs undergoing hip arthroplasty.

Study design Investigator-blind, controlled, randomized, prospective clinical trial.

Animals Twenty client-owned dogs undergoing hip arthroplasty were allocated randomly to either group C (control, 1 mg kg^{-1} epidural ropivacaine) or group M (magnesium, epidural injection of 1 mg kg^{-1} ropivacaine and 2 mg kg^{-1} magnesium sulphate).

Methods All dogs were premedicated with intramuscular acepromazine. General anaesthesia was induced with propofol, and maintained with isoflurane in oxygen. Intraoperatively, nociception was assessed based on changes in heart rate, respiratory rate, and mean arterial pressure above baseline values. Postoperatively, pain was evaluated with a Sammarco pain score, a Glasgow pain scale and a visual analogue scale. The Tarlov's scale was used to quantify motor block. All dogs were evaluated at recovery and then 1, 2, 3, 4, 5 and 24 hours after that. Rescue analgesia was provided during surgery with fentanyl and, postoperatively, with buprenorphine. Groups were compared using one way repeated measures analysis of variance followed by Holm-Sidak method for multiple comparison, or non-parametric tests when appropriate.

Results The two treatment groups did not differ ($p > 0.05$) with respect to intraoperative physiological variables, rescue analgesia, postoperative pain scores (Sammarco q =

1.00; Glasgow q = 3.10; VAS q = 0.50) and duration of the motor block (Tarlov's q = 2.40).

Conclusions and clinical relevance The addition of epidural magnesium to ropivacaine did not improve or prolong the analgesia provided by ropivacaine alone. Further studies are needed to determine whether an epidural magnesium dose higher than 2 mg kg^{-1} would exert better analgesia, without causing adverse effects, in dogs undergoing orthopaedic surgery.

Keywords dog, magnesium sulphate; neuroaxial anaesthesia, perioperative analgesia, ropivacaine

Introduction

Total hip replacement is an innovative and invasive surgery used in dogs to treat hip dysplasia and other pathological conditions affecting the coxofemoral joint. Providing adequate perioperative analgesia during invasive orthopaedic procedures not only is an ethical obligation for the veterinarian, but also plays a crucial role in the outcome of the surgery itself (Conzemius et al. 2005). Indeed, effective prevention and treatment of pain has been shown to significantly improve dogs' attitude, as well as limb's use and function in dogs undergoing major orthopaedic surgery (Conzemius et al. 2005).

As an alternative to systemic analgesia, loco-regional anaesthetic techniques offer the advantage of a selective and targeted block of the anatomical area of interest. Among neuroaxial techniques, epidural administration of analgesics is traditionally regarded as safer and easier to perform than the spinal route. Owing to its popularity, practicality and ease of performance, single epidural injection is usually preferred to constant rate infusion of analgesics via this route, which can only be accomplished after insertion of an epidural catheter. Placing an epidural catheter is a time-consuming procedure, which requires a certain degree of expertise and carries the risk of complications (Ladha et al. 2013; Pumberger et al. 2013). Nevertheless, single epidural injections may provide analgesia of insufficient duration when invasive and potentially long surgeries are performed.

Within the last twenty years, there has been an increasing interest in the multimodal approach to pain management in veterinary patients, especially with respect to the use of agents which, despite not being listed among classical analgesics, exert antinociceptive effects (Kukanich 2013; Madden et al. 2014; Crociolli et al. 2015; Norkus et al. 2015). Among these, magnesium plays a central role in the prevention of central sensitization by blocking the dorsal horn N-methyl-D-aspartate (NMDA) receptors in a non-competitive, voltage dependent fashion. Magnesium sulphate is inexpensive, and available in Europe as a formulation that is stable at room temperature and approved for parenteral administration in dogs. The potential for neurotoxicity when magnesium is administered intrathecally was investigated in dogs, and neurological impairment and histopathological lesions of the spinal cord were not found after a dose of 3 mg kg^{-1} (Simpson et al. 1994). The studies investigating the clinical role of magnesium as adjuvant in pain therapy show conflicting results. Intravenous magnesium failed to improve perioperative pain in both humans and dogs (Rioja et al. 2012; Murphy et al. 2013). Conversely, several clinical trials showed that magnesium effectively improves analgesia in human patients receiving combinations of local anaesthetics and opioids, by either epidural or spinal route (Buvanendran et al. 2002; Oezalevli et al. 2005; Arcioni et al. 2007). The antinociceptive effects of epidural magnesium were demonstrated experimentally in dogs (Bahrenberg et al. 2015), however there is a paucity of data regarding the clinical use of magnesium in this species. A clinical trial suggests that adding spinal magnesium to ropivacaine increases the duration and the intensity of analgesia, but also of the motor block, provided by ropivacaine alone in dogs undergoing orthopaedic surgery (Adami et al. 2016).

The aim of this study was to determine whether the addition of magnesium sulphate to epidural ropivacaine would result in better perioperative analgesia, defined as longer duration and decreased rescue analgesia requirement, than ropivacaine alone, in client-owned dogs anaesthetised for elective hip arthroplasty.

Our hypothesis was that the addition of magnesium to ropivacaine would improve perioperative analgesia, without prolonging the motor block or causing neurological dysfunction of the hind limbs.

Materials and methods

This clinical study was designed as an investigator-blind, controlled, randomized, prospective trial.

Twenty client-owned dogs scheduled for hip arthroplasty between March 2014 and February 2016 were recruited for this study. The number of dogs was determined based on a sample size calculation. Each group was to be composed of a minimum of 10 dogs to detect, with one-way analysis of variance (with power equal to 0.95 level of confidence and α value and standard deviation set at 0.05 and 40 minutes, respectively), a difference between groups in the mean duration of analgesia (defined as the time from the epidural injection to the administration of the first dose of rescue analgesic agent) equal to at least 60 minutes.

Inclusion criteria were American Society of Anaesthesiologists (ASA) risk category lower than III and absence of skin infections at the level of the lumbosacral area. All dogs underwent a preanaesthetic physical examination and a complete blood test, including haematology and biochemistry, to rule out abnormalities. The permission of

the Ethical Committee of the Veterinary Teaching Hospital of the University of Turin (Italy), as well as a written consent signed by the dogs' owners, was obtained prior to enrolment.

All dogs were premedicated with intramuscular (IM) acepromazine (0.03 mg kg^{-1}, Prequillan; Fatro, Italy). Thereafter, intravenous (IV) propofol (Vetofol; Esteve, Spain) was titrated to effect to induce general anaesthesia. After orotracheal intubation, isoflurane (Isoflo; Esteve, Spain) was delivered in oxygen via a circle system and lactated Ringer's solution was perfused IV (10 mL kg^{-1} hr^{-1}, Ringer Lattato; Fresenius Kabi, Italy). Arterial blood pressure [systolic (SAP), mean (MAP) and diastolic (DAP)] was measured continuously through an indwelling catheter placed in the dorsal pedal artery. Monitoring during anaesthesia included both cardiovascular [SAP, MAP, DAP, heart rate (HR) and rhythm) and respiratory [end tidal carbon dioxide ($P_E´CO_2$), peak inspiratory pressure (PIP), respiratory rate (f_R), tidal volume (V_T), minute volume (V_E), inspired fraction of oxygen (FIO_2), end tidal isoflurane tension ($P_E´ISO$]) parameters, as well as oesophageal temperature (T°, C). Manual data recording was performed every 5 minutes for the entire duration of anaesthesia. Spontaneous breathing was preferred unless $P_E´CO_2$ reached more than 45 mmHg (5.9 kPa) when mechanical ventilation was used to maintain normocapnia. The target $P_E´ISO$ was 1.3%, which is equal to the Minimum Alveolar Concentration (MAC) as determined in dogs (Valverde et al. 2003).

As soon as the anaesthesia plane was deemed surgical based on classical clinical parameters (relaxation of the jaw, absence of blinking and movements, light palpebral reflex and normal canine physiological parameters) the anaesthetist (EL), who was unaware of the epidural treatment, performed all the epidural injections.

The dogs were positioned in sternal recumbency with the hind limbs cranial to maximize the dorsal lumbosacral space. The ilium wings, together with the sacrum and the dorsal spinous processes of L6 and L7, were used as anatomical landmarks. After surgical preparation of the area, a 75 mm, 19 gauge spinal needle (BD Needles; Becton Dickinson, Spain) was inserted percutaneously between L7 and S1, with the bevel facing cranial, and then advanced through the intervertebral ligament into the epidural space. Both the "popping" sensation, perceived while penetrating the interarcuate ligament, and the hanging drop technique with saline were used as a first assessment of proper needle placement. Radiographic exam followed to confirm correct positioning of the needle between L7 and S1. A horizontal beam was used to maintain positioning in sternal recumbency during injection.

A block randomization method was used to allocate the dogs into one of two epidural treatment groups. Briefly, an operator not participating to the assessments was in charge of keeping an opaque, sealed envelope from which treatment assignments were shuffled and drawn. This same operator was also responsible for the list of allocations until the end of data collection.

Epidural ropivacaine (Naropina 0.5%; AstraZeneca, Italy), 1 mg kg^{-1} (volume: 0.2 mL kg^{-1}), was administered epidurally to group C (Control), while group M (Magnesium) was treated with ropivacaine (1 mg kg^{-1}; volume: 0.2 mL kg^{-1}) and magnesium sulfate (Magnesio Solfato 2g 10 mL^{-1}; Galenica Senese, Italy) at the dose of 2 mg kg^{-1} (volume: 0.01 mL kg^{-1}). The drugs were mixed in the same syringe and administred as a single bolus over 1 minute. Doses were chosen based on the authors' past clinical experience, and human and veterinary medical literature (Arcioni et al. 2007; Bilir et al.

148 2007; Oezalevli et al. 2005). After the epidural injection was performed, the dogs
149 remained in sternal recumbency for 5 minutes.

150 A bolus of IV atropine (0.01 mg kg^{-1}, Atropina Solfato; ATI, Italy) was injected in the
151 event of bradycardia (<45 beats minute-^{1}). Treatment of hypotension (MAP <60
152 mmHg) consisted of an IV bolus of lactated Ringer's solution (10 mL kg^{-1} over 10
153 minutes), followed by an IV colloid bolus (Voluven; Fresenius Kabi, Italy; 2 mL kg^{-1}
154 over 10 minutes), and then by an IV infusion of dopamine (Revivan; AstraZeneca, Italy;
155 starting at 10 µg kg^{-1} $minute^{-1}$, increased in increments of 2.5 µg kg^{-1} $minute^{-1}$ every 10
156 minutes until MAP increased above 60 mmHg) in the event of unresponsive
157 hypotension. Bradyarrhythmias and hypotension occurring shortly after the epidural
158 injection were regarded as clinical symptoms compatible with either sympathetic nerve
159 blockade or hypermagnesaemia, and their occurrence was recorded.

160 Intraoperative nociception was defined as an increase in HR, MAP and/or f_R of at least
161 20% compared to the baseline (recorded before skin incision, after $P_{E'}$ISO had been
162 maintained constant at 1.3% for at least three consecutive measurements, over 15
163 minutes). When two of these three parameters increased above the defined values,
164 rescue fentanyl (Fentanest; Pfizer, Italy) was administered IV (0.003 mg kg^{-1}).

165 The duration of surgery and of anaesthesia (minutes) were recorded. The time elapsed
166 from termination of inhalational anaesthesia to recovery in intensive care unit (minutes)
167 was defined as "time to recovery", and recorded. The trachea was extubated after return
168 of swallowing and palpebral reflexes, accompanied by increased jaw tone. At this point,
169 all dogs were administered with IV carprofen (4 mg kg^{-1}, Rimadyl; Pfizer, Italy).

Postoperatively, a multifactorial pain score modified from Sammarco ranging from 0) no pain to 13) extreme pain (Appendix 1; Sammarco et al. 1996; Adami et al. 2012) and the short form of the Glasgow pain scale ranging from 0) no pain to 20) extreme pain (Holton et al. 2001) were used to evaluate pain. Additionally, a 10 cm visual analogue scale (VAS) with end points labelled 0) worst possible pain to 10) absence of pain was utilized. Rescue analgesia consisted of 0.01 mg kg^{-1} buprenorphine IV (Temgesic; Schering Plough, UK), administered when at least one pain score was 40% or more of the maximum value of the scale (<6 for the VAS, >5 for the multifactorial pain score scale, >8 for the Glasgow pain scale). A modified Tarlov's scale (Appendix 2) ranging from 0) neurological impairment to 4) no signs of motor block (Buvanendran et al. 2002; Adami et al. 2016) was used for neurological assessment of the hind limbs and quantification of motor blockade. The same observer (EL), who was unaware of the treatment, performed all the evaluations. All dogs were evaluated when deemed awake enough to respond to vocal call and incitement to sit or stand up, and then 60, 120, 180, 240, 300 minutes and 24 hours after the end of surgery and before being discharged from the hospital.

Statistical analysis was accomplished with commercially available software (SigmaStat and SigmaPlot 12, Systat Software Inc.). Normality of data distribution was assessed with the Kolmogorov-Smirnov test and with the Shapiro-Wilk test. Continuous variables were analysed with either one way repeated measures analysis of variance followed by Holm-Sidak method for multiple comparison, or Friedman repeated measures analysis of variance on ranks followed by Tukey test, where it applied. For the analysis of intraoperative cardiovascular and respiratory variables, only the values

193 recorded during three significant events were used: 0) before surgery (baseline as above
194 described), 1) 30 seconds after skin incision and 2) during femoral head osteotomy.

195 For non-continuous variables, either a T-test or Mann Whitney Rank Sum test were
196 used. Within each treatment group, the proportions of dogs which experienced
197 hypotension and bradyarrhythmias following epidural injection of magnesium were
198 analysed with the Fisher exact test. P values < 0.05 and q values < 2 were considered
199 statistically significant.

200

201

202 **Results**

203 Data are presented as either mean ± standard deviation or median (range). Twenty dogs
204 (12 female and 8 male) of various breeds, aged 12 (9-144) months completed this study.

205 Heart rate, MAP, time to recovery and duration of anaesthesia were normally
206 distributed. Anaesthesia was uneventful in all dogs enrolled in the study and lasted 222
207 ± 62 minutes in group M and 220 ± 32 minutes in group C, respectively; this difference
208 was not statistically significant. The treatment groups were not statistically different to
209 each other with respect to intraoperative physiological variables. However, HR
210 decreased over time in the control group while MAP increased in both groups (Fig. 1).
211 Respiratory rate increased over time in group M while it decreased in group C (Fig. 1).
212 Cardiovascular events compatible with hypermagnesaemia, namely bradyarrhythmias
213 and hypotension, were not observed during the anaesthetics. Three dogs of group M [0
214 (0-1)] and 4 of group C [0 (0-2)] required boluses of rescue fentanyl during surgery.
215 This difference was not statistically significant. There was no difference in the duration

of surgery, which lasted 120 (90-150) and 125 (100-150) minutes in groups M and C, respectively, was detected between groups. Only one dog, assigned to group C, required rescue buprenorphine before completion of pain assessments according to both the Sammarco and VAS scores (7 and 6.8, respectively).

There was no significant difference between groups C and M in the VAS, Sammarco, Glasgow and Tarlov's scores. In both groups, the Sammarco, the Glasgow and the Tarlov's scores significantly increased over time, while VAS decreased (Fig. 2).

Recovery was smooth and normal motor function of the hind limbs was observed within 6 hours of the epidural injection in all dogs. Perianaesthetic complications were not observed.

Discussion

This study failed to demonstrate that the addition of magnesium to epidural ropivacaine provides superior perioperative analgesia, in terms of both duration and quality, than ropivacaine alone in dogs undergoing total hip replacement. The duration of the motor block was also comparable between the two groups, and the administration of magnesium was not associated with neurological dysfunction of the hind limbs.

These findings were unexpected and not consistent with those of a previous study, which found that the addition of spinal magnesium to ropivacaine potentiated the intensity and the duration of analgesia in dogs after tibial plateau levelling osteotomy (Adami et al. 2016), but also prolonged the duration of the motor block.

Possible explanations for this discrepancy are less effective analgesia when magnesium is administered epidurally compared to the spinal route or, alternatively, a failure in the methods used in the current study to detect a difference between treatments.

Besides the possibility of a direct analgesic effect of magnesium on the dorsal horn NMDA receptors, Adami and colleagues (2016) hypothesized that the ionized magnesium released by its salt may exert antinociception also by blocking the calcium channels, which in turn could alter the resting potential of the neuronal membranes. Alternatively, as a hyperosmolar salt, magnesium sulfate might cause osmotic interference with the cerebrospinal fluid and spinal cord, leading to neuronal shrinking and transient neurologic dysfunction (Busselberg et al. 1994). However, this hypothesis could not be tested because the actual osmolality of the solution to be injected could not be measured. Moreover, both mechanisms are more likely to occur when magnesium is injected spinally rather than epidurally because we suspect that a higher concentration is achieved in the cerebrospinal fluid when the dose is injected spinally.

Another reasonable explanation is that the epidural route of administration requires a higher magnesium dose than the spinal one in order to detect appreciable analgesia. Owing to ethical obligations, and not to cause any harm to client-owned dogs, it was decided to use 2 mg kg^{-1} magnesium. This dose was proven to be safe in terms of risks of direct neurotoxicity (Simpson et al. 1994) and hypermagnesaemia (Adami et al. 2016). Nonetheless, it cannot be excluded that a higher magnesium sulfate dose might have resulted in more pronounced clinical effects.

Pain assessment in non-verbal patients can be extraordinarily challenging even for experienced observers, especially when subjective indicators, namely behavioural signs of pain, are evaluated (Conzemius et al. 1997; Reid et al. 2007). The choice of having one single investigator in charge of all the assessments, as well as of using several pain scales instead of one, should have helped overcome some potential intrinsic limitations, namely the interobserver variability and the poor sensitivity and specificity of the scales used to evaluate pain.

Lower pain score intervention levels might have resulted in detectable differences in postoperative analgesia between treatments. For consistency, it was decided to use the same cut-off value for all pain scales, which was set at 40% of the maximum possible score. Similar cut-off values of the VAS have been previously used in dogs, as well as in other animal species, to guide the administration of rescue analgesics during the postoperative period (Adami et al. 2011; Adami et al. 2012). Moreover, it has been suggested that, in human patients, 40% of the VAS scale may represent the limit between mild and moderate pain (Serlin et al. 1995; Bodian et al. 2001;).

Another potential limitation of this study is the absence of irrefutable proof that the needle had been correctly placed within the epidural space in all dogs. Although the hanging drop technique was used to guide the needle's insertion, and radiography to verify the needle's position within the targeted intervertebral space, only epidurography, accomplished with the injection of a contrast medium, would have inarguably confirmed that the tip of the needle had reached the adequate depth. Due to ethical considerations for the client-owned dogs, the use of invasive or potentially harmful techniques for this purpose was not considered. Failure to identify the exact injection site could have distorted the results; however, the little or no postoperative rescue

analgesia requirement, together with the detection of motor blockade in all dogs at recovery, suggests that the epidural injections were correctly performed.

Assuming that all the injections had been performed within the epidural space, an alternative possible explanation for the lack of differences between the two treatments is that ropivacaine alone, at the dose and concentration used in the current study, might already be adequate as analgesic treatment for hip replacement. Moreover, carprofen was administered to all dogs in recovery, which could have contributed to postoperative analgesia and made the detection of differences between groups even more challenging. In this scenario, detecting an appreciable difference would be more challenging and possibly require a larger sample size. Unfortunately, the use of a suboptimal analgesic treatment, namely a subclinical ropivacaine dose or even epidural saline, would have raised some ethical concerns.

Serum magnesium concentrations were not measured. Although mild increases in ionised magnesium concentration might have gone undetected, it is reasonable to assume that a clinically relevant hypermagnesaemia would have been accompanied by cardiac arrhythmias and, possibly, persistent hypotension, none of which were observed in this study population. Moreover, one study found that 2.5 mg kg^{-1} of epidural magnesium did not result in clinical signs of hypermagnesaemia in dogs (Bahrenberg et al. 2015).

Conclusions

In conclusion, the addition of 2 mg kg^{-1} magnesium sulphate to epidural ropivacaine did not result in considerable improvement of quality and duration of perioperative analgesia, nor did it prolong the motor block. Further trials are needed to determine whether a higher dose of magnesium administered via the epidural route would increase the analgesic effect in dogs undergoing orthopaedic surgery.

Conflict of interest statement

None of the authors have financial or personal relationships with individuals or organisations that could inappropriately influence or bias the content of the paper.

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Appendix 1

Modified multifactorial pain score (Sammarco et.al., 1996; Adami et al., 2012) to assess post-operative pain in 20 dogs undergoing total hip replacement.

The same observer who was blind to the treatment evaluated the dogs as soon as they were awake enough to respond to stimulation (vocal call and incitement to sit or stand up) and then 60, 120, 180, 240, 300 minutes and 24 hours after surgery.

Vocalization								
-None	0	0	0	0	0	0	0	0
-Intermittent vocalization	1	1	1	1	1	1	1	1
-Continuous vocalization	2	2	2	2	2	2	2	2
Movement								
-None	0	0	0	0	0	0	0	0
-Frequent position changes	1	1	1	1	1	1	1	1
- Rolling, thrashing	2	2	2	2	2	2	2	2
Agitation								
-Calm	0	0	0	0	0	0	0	0
-Mild agitation	1	1	1	1	1	1	1	1
-Moderate agitation	2	2	2	2	2	2	2	2
-Severe agitation	3	3	3	3	3	3	3	3
Heart rate								
-1-15% above preoperative value	0	0	0	0	0	0	0	0
-16-29% above preoperative value	1	1	1	1	1	1	1	1
-30-45% above preoperative value	2	2	2	2	2	2	2	2
->45% above preoperative value	3	3	3	3	3	3	3	3
Respiratory rate								
-1-15% above preoperative value	0	0	0	0	0	0	0	0
-16-29% above preoperative value	1	1	1	1	1	1	1	1
-30-45% above preoperative value	2	2	2	2	2	2	2	2
->45% above preoperative value	3	3	3	3	3	3	3	3
Total (0-13)								

Appendix 2

Modified Tarlov's scale (Buvanendran et al., 2002; Adami et al., 2016) to evaluate the neurological function of the hind limbs and the degree of motor blockade in 20 dogs undergoing total hip replacement.

The same observer who was blind to the treatment evaluated the dogs as soon as they were awake enough to respond to stimulation (vocal call and incitement to sit or stand up) and then 60, 120, 180, 240, 300 minutes and 24 hours after surgery.

Grade 0	Flaccid paraplegia, no movements of the hind limbs, possible loss of bowel/ urinary bladder control
Grade 1	Spastic paraplegia with moderate or vigorous purposeless movements of the hind limbs. No sitting, unable to walk
Grade 2	Good movements of the hind limbs but unable to stand
Grade 3	Able to stand but unable to walk normally; hips and limbs obviously unstable, moderate to severe ataxia
Grade 4	Able to stand and walk normally, some muscle weakness of the hind limbs may be seen

Figure legends

Figure 1 Intraoperative physiological variables recorded from 20 dogs anaesthetized for total hip replacement and assigned to one of two treatment groups: group C (Control, epidural ropivacaine; *n* = 10) and group M (Magnesium, epidural combination of magnesium and ropivacaine; *n* = 10). Data are presented as mean ± standard deviation. 0: values recorded as baseline in the anaesthetized dogs prior to surgical stimulation; 1: values recorded immediately after skin incision; 2: values recorded after femoral head osteotomy.

Footnotes:

Mean arterial pressure

†Significantly different from baseline for Group M (p value < 0.05, q value = 8.80)

‡Significantly different from baseline for Group C (p value < 0.05)

Respiratory rate

†Significantly different from baseline for Group M (p < 0.05, q > 8.00)

‡Significantly different from baseline for Group C (p < 0.05, q = 8.40)

Figure 2 Postoperative pain scores recorded from 20 dogs anaesthetized for total hip replacement and assigned to one of two treatment groups: group C (Control, epidural ropivacaine; *n* = 10) and group M (Magnesium, epidural combination of magnesium and ropivacaine; *n* = 10). Data are presented as medians and interquartile ranges (25%-75%). 1: values recorded after recovery, as soon as the patients were able to sit and respond to vocal call; 2, 3, 4, 5 and 6 are 60, 120, 180, 240, 300 minutes and 24 hours after recovery.

Footnotes

Sammarco score

†Significantly different from baseline for Group M (p value < 0.05)

‡Significantly different from baseline for Group C (p value < 0.05)

Visual Analogue Scale score

†Significantly different from baseline for Group M (p value < 0.05, q value = 12.16)

‡Significantly different from baseline for Group C (p value < 0.05, q value = 11.65)

Tarlov's score

†Significantly different from baseline for Group M (p value < 0.05)

‡Significantly different from baseline for Group C (p value < 0.05)