6-1-2012

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Original Article

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Abstract

Objective: To evaluate midazolam as an epidural analgesic in patients undergoing single-level microdiscectomy.

Methods: This prospective case control study was carried out at the Aga Khan University Hospital, Karachi, from January 20 to September 20, 2007, on patients undergoing microdiscectomy. Cases (group A) received midazolam with saline, while controls (group B) received saline only, placed intra-operatively over involved nerve root. Post-operatively, patients were monitored for various variables. Data was analysed using SPSS 13.0 and groups were compared using student's t-test for continuous variables and chi square for categorical variables. P-value <0.05 was considered significant.

Results: Patients in group A ambulated earlier (p = 0.005) and although they did not show significantly better post-operative pain control, but post-operative nausea and vomiting (PONV) score was better at six hours (p = 0.020). There was no difference in other variables such as requirement of analgesics, anti-emetics, hospital stay and complications.

Conclusion: Midazolam may improve post-operative nausea and vomiting score, and may lead to earlier ambulation, without affecting patient's vitals, consciousness, lower extremity power or sensations, and is not associated with adverse effects.

Keywords: Microdiscectomy, Midazolam, Epidural analgesia, Post-operative pain (JPMA 62: 561; 2012).

Introduction

Microdiscectomy (MD) is the surgical removal of prolapsed intervertebral disc, and is one of the most commonly performed neurosurgical procedures in the world with excellent results and minimum morbidity.[1] Post-operative pain remains the major reason for increased hospital stay, days off work, and delay in ambulation in these patients and various methods have been proposed to minimise post-operative pain.[2,3] Epidural analgesia is widely used for post-operative pain in a variety of surgical procedures and is recognised to provide superior quality of analgesia when compared with systemic opioids.[4] Midazolam, a water soluble benzodiazepine, produces an analgesic action through the benzodiazepine/gamma

aminobutyric acid (GABA) receptor complex in the spinal cord. Reported first around 1978, it is extensively used as a systemic adjuvant in operating rooms and critical care medicine for its sedative, anxiolytic and amnesic effects.[5] Its systemic actions and benzodiazepine pharmacology have been comprehensively studied and are now very well understood.[5] Recently, its use has been extended to epidural and intrathecal routes with considerable success without any reported adverse effects.[6-8] Since midazolam also enjoys widespread availability, low cost and excellent patient tolerance, we hypothesise that it would be an ideal analgesic when used as an intra-operative nerve root and thecal sac irrigant in patients undergoing microdiscectomy for prolapsed lumbosacral intervertebral disc. Positive results would help to establish midazolam as an analgesic in all spine surgeries that involve exposure of epidural space. This study was undertaken to evaluate medazolam in patietns undergoing microdiscectomy.

Patients and Methods

This is a prospective case control study conducted from January 20 to September 20, 2007, at Aga Khan University Hospital, Karachi, following approval by the hospital's ethics review committee. All adult patients admitted for single level (L4-5 or L5-S1) microdiscectomy were included. Patients who were excluded were those who either had symptoms for more than six months, spinal canal stenosis, previous history of spine surgery, were known to have contraindications to midazolam or who were unable to complete the Visual Analogue Scale (VAS). Surgical procedures with intra-operative dural tear or nerve root damage were also excluded. Patients were enrolled during the study period in one of the two groups; A (case group), and B (control group), by non-probability, convenience sampling. Thirty patients were included in each group. Patients in group A (case group) received a 2 centimetre x 2 centimetre absorbable gelatin sponge (Gelfoam, Upjohn Co., Kalamazoo, MI) soaked in 1 milligram per 1 milliliter midazolam diluted in 1 milliliter 0.9 % isotonic saline. Patients in group B (control group) received a similar gelfoam soaked in 0.9 % isotonic saline alone which was placed over the exposed nerve root and adjacent thecal sac after having had a standard microdiscectomy. These gelfoam pieces are absorbable and, therefore, were not removed, and the placement was followed by wound closure. All surgeries were performed in general anaesthesia. All efforts were made to standardise the procedure and post-operatively patients were managed within a standardised protocol of medications. Additional analgesic and anti-emetic requirements were met with intravenous Ketorolac 30 mg and intravenous Metoclopromide 10 mg respectively. All patients were serially monitored for pain and side effects at 1 hour, 6 hours, 12 hours, 24 hours and 48 hours post-operatively, using VAS for pain and a pre-designed pro-forma for potential side effects. Post-operative nausea, vomiting (PONV), sedation and degree of ambulation, lower extremity sensations, power and post-operative complications were also recorded using standardised scoring systems.

The data thus collected were entered and analysed using SPSS version 13.0 (Chicago, IL, USA). Results are expressed as mean ± standard deviation for continuous variables and frequency/percentage for categorical data. Cases and controls were compared using independent sample student's t-test for continuous variables and chi square for categorical variables. Tables (2x2) were used to calculate Odd's ratios and $p = <0.05$ was considered significant.

Results

There were no dropouts from the study and both groups were comparable in terms of gender distribution, mean age ($p = 0.89$), duration of symptoms ($p = 0.152$), operative time ($p = 0.469$) and hospital stay ($p = 0.623$). Mean VAS of the two group of patients at different observation times was noted (Table-1). The difference in post-operative pain at one hour ($p = 0.451$), six hours ($p = 0.6$), 12 hours ($p = 0.44$), 24 hours ($p = 0.96$) and 48 hours ($p = 0.15$) were not statistically significant. By the end of first hour post-surgery, 21 (70%) patients in group A and 10 (33.3%) patients in group B were able to ambulate without assistance (Table-2). This difference was statistically significant ($p = 0.005$, OR 0.2143, CI 95%). All of our patients were mobilised without support by the 12th post-operative hour. None of the patients in the study showed any reduction in their hip joint power or lower extremity temperature sensations or pre-operative Straight Leg Raising

Table-1: Comparison of post-operative pain (VAS).

	Group A (Cases)			Group B (Controls)			
	Mean	S D	Range	Mean	S D	Range	P-value
1 hour	5.57	2.16	2-10	6.07	1.98	2-10	0.45
6 hours	4.23	1.54	2-7	4.47	1.43	2-7	0.6
12 hours	3.17	1.05	1-5	3.20	0.96	1-5	0.44
24 hours	2.60	0.77	1-4	2.57	0.77	1-4	0.96
48 hours	2.13	0.93	1-4	2.03	0.76	1-3	0.15

VAS: Visual Anologue Scale.

Table-2: Comparison of post-operative unassisted ambulation (n = no. of patients).

	Group A (Cases)	Group B (Controls)	P-value	Odds Ratio	Pearson Chi -square	Confidence Interval (%)
1 hour	21 (70%)	10 (33.3%)	0.005	0.214	8.08	95
6 hours	26 (86.6%)	28 (93.3%)	0.335	2.153	-	95
>6 hours	30 (100%)	30 (100%)	-	-	-	-

Table-3: Comparison of PONV score.

		Group A (Case group)	Group B (Control group)	P-value	Odds Ratio	Pearson Chi -square	Confidence Interval (%)
At 1 post-operative hour	PONV 1	18 (60%)	15 (50%)	0.642	0.667	0.61	95
	PONV 2	9 (30%)	13 (43.3%)				
	PONV 3	3 (10%)	2 (6.6%)				
At 6 post-operative hours	PONV 1	30 (100%)	23 (76.6%)	0.020	0	-	95
	PONV 2	0 (0%)	5 (16.6%)				
	PONV 3	0 (0%)	2 (6.6%)				

PONV: Post-operative Nausea and Vomiting.

(SLR) at any point in their post-operative course. Sedation scores (p = 0.072) and PONV score (p = 0.642) at one hour were also not significant. Both these differences however, become important at six hours (Table-3). Differences in mean heart rates at one hour (p = 0.282), six hours (p = 0.933), 12 hours (p = 0.470), 24 hours (p = 0.924) and later, were statistically insignificant. Differences in the requirement of rescue analgesia at one hour (p = 0.206), six hours (p = 0.119) and later were similarly insignificant. A total of six (10%) patients went into post-operative urinary retention, three in each group, all responding to non-invasive manoeuvres and none requiring catheterisation.

Discussion

Microdiscectomy can be performed as a daycare procedure and is being done so at a number of centres around the world. Post-operative pain remains the major reason for increased hospital stay, days off work, and delay in ambulation in these patients. Patients usually report resolution of pre-operative leg pain, but report new onset, post-operative back pain focused mainly at the incision site. This pain is thought to be due to the skin and fascial incision, muscle retraction and laminotomy; and various methods have been proposed to minimise it.[2-4] Delivery of medications directly into the epidural space provides better pain control and improves perioperative pathophysiology, resulting in decreased post-operative morbidity.[9,10] Meta-analysis has shown that epidural analgesia is superior to parenteral opioids for each post-operative day, for all types of surgeries and all types of pain assessment methods.[11] The complication rates are lower and the most commonly reported complications include urinary retention, hypotension, lower extremity motor blockade, paresthesias, epidural bleeding, infection, nausea, vomiting and headaches. Epidural analgesia is liable to failure mostly due to technical complications involved in the administration of drug through lumbar puncture needle or fine epidural catheter. Exposure of epidural space during microdiscectomy provides an excellent opportunity to administer these medications without the risk of complications that include bleeding, cerebrospinal fluid (CSF) leak with accompanying post-dural puncture headaches or inadvertent intra-thecal administration.

Midazolam is extensively used as a systemic adjuvant in operating rooms and also in critical care medicine. Its systemic actions and pharmacology have been comprehensively studied and are very well understood. Its clinical use has been extended to epidural and intra-thecal routes with success and without adverse effects.[5] It has been shown that within the spinal cord, both the inhibitory neurotransmitter gamma aminobutyric acid (GABA) and the excitatory neurotransmitter glutamate are involved in nociceptive mechanisms and may operate in concert.[12,13] The GABAA receptors are proposed to exist at the primary afferent terminal in the spinal cord; and the GABAergic system has been proposed to play an important role in the presynaptic inhibition of primary afferents. Interestingly, GABAA receptor (Cl- channel) in the spinal cord also possess benzodiazepine binding sites.[14] These benzodiazepine receptors are concerned with pain transmission in the dorsal horn of the spinal cord by increasing the Cl- conductance of GABAA on the primary afferents, hyperpolarising it and, therefore, reducing the release of glutamate in the spinal cord.[14,15] Benzodiazepine receptor agonists increase the intrinsic efficacy of GABA at the GABAA receptor coupling with benzodiazepine receptor in the spinal cord. Thus, both benzodiazepines and benzodiazepine receptor agonists may exhibit spinally mediated anti-nociceptive effects.[14,16,17] These observations

have led to a number of experiments further suggesting the action of benzodiazepine and its agonists. Nishiyama reports that midazolam, which is itself a water soluble benzodiazepine derivative by virtue of being a benzodiazepine-GABAA receptor complex agonist, exhibits synergistic analgesia for thermally-induced acute nociception as well as persistent inflammatory nociceptive activation both with N-Methyl-DAspartica Acid (NMDA) and 2-amino-3-(5-methyl-3-oxo-12-oxazol-4-yl) Propanoic Acid (AMPA) receptor antagonists.[18] Goodchild et al also reported that intra-thecal midazolam caused spinally mediated anti-nociception by a mechanism involving opioid receptor activation, and Bahar et al showed its anaesthetic affects.[19,20]

Gibbons et al[21] proposed using absorbable gelatin sponge contoured to the laminotomy defect, soaked in methylprednisolone acetate and preservative-free morphine, and concluded that this method provides effective, safe and extended analgesia after lumbar discectomy. We used the same method to deliver midazolam to our patients. The mean age of patients included in our study was 38 years which is consistent with literature.[1] Published literature does not support any gender predisposition for intervertebral disc herniation, but in our study we found an overwhelming male predominance (68% male patients), consistent with other local studies showing male predisposition in pathologies which otherwise are not known to show gender predilection.[22-24] Mean VAS at one hour post-surgery was more for patients in group B (6.07) as compared to patients in group A (5.57), possibly suggesting some degree of analgesia provided by the epidural midazolam. The VAS thereafter showed gradual decline at 6, 12, 24 and 48 hours and the difference between groups becomes insignificant. On analysis of post-operative ambulation, we found that patients who were administered midazolam were able to initiate ambulation much earlier as compared to the other group. This became a significant difference ($p = 0.005$). By the sixth post-operative hour, 54 (90 %) of the patients were mobile without any support and the difference became less significant ($p = 0.335$).

Side effects of midazolam are unusual and mostly seen with large intravenous or oral ingestion, and include sedation and amnesia. Studies have ruled out any potential for neurotoxicity if the dosage is kept within the safety range.[5,7,8,18-22] Nishiyama experimented with epidurally administered midazolam in dogs and measured serial serum and cerebrospinal fluid drug concentrations and concluded that the cerebrospinal fluid concentrations are only 3% of those in the systemic circulation.[7] Other potential adverse effects include changes in spinal somatosensory evoked potentials, which have also been disregarded on the basis of several well-conducted human and animal studies.[5,8,27-29] Repeated motor and sensory examinations carried out in all our patients also ensured no alterations in axonal transport. Sedation was monitored using the Ramsay scale and only two patients showed any degree of sedation, suggesting that epidural midazolam had no effect on sedation. Blood pressure monitoring was also carried out in all patients and no significant alteration in haemodynamics was found. Post operative nausea and vomiting was measured using the PONV scoring system described by Wilson et al and later used by Pandey et al.[29] There are several studies which suggest that midazolam, when used pre-operatively, significantly reduces post-operative nausea and vomiting when administered either per oral or as intravenous formulations.[30,31] On comparing the two groups, nine (30%) patients in group A and 13 (43.3 %) in group B had mild nausea or single emetic episode (PONV score 2) at the end of first post-operative hour. Apart from these, three (10 %) patients in group A and 2 (6.6 %) in group B also had one or two emetic episodes or moderate to severe nausea requiring anti-emetic therapy (PONV score 3). However, at the end of the sixth post-operative hour, no patient in group A and five (16.6 %) in group B had PONV score of 2 ($p = 0.020$). These results suggest that midazolam may have an affect on PONV at one and six hours ($p = 0.642$ and 0.020 respectively). The only complication noticed in the study was post-operative urinary retention. None of the patients in our study showed any reduction in their hip joint power or lower extremity temperature sensations at any point in their post-operative course.

The investigator most noted for his work on midazolam as an epidural analgesic is Nishiyama.[6,7,18] Most of his work is done on patients undergoing abdominal surgery. He has concluded that epidural midazolam increases the central analgesic, sedative and amnesic effects of spinal analgesia and is useful for managing post-operative pain. In all of these studies epidural midazolam did not show any effect on patient's haemodynamics just as was the case in our study. We used much lower doses of midazolam as compared to Nishiyama et al, as the post-operative analgesic requirements following microdiscectomy are far lower than those following abdominal surgery.[6,7,18] In Nishiyama's studies, the investigators were able to achieve better post-operative pain control as compared to our study, though at the expense of more sedation.[6,7,18] Such an effect may be desirable after upper abdominal surgery, but after microdiscectomy when early ambulation is the goal, pain relief at the expense of sedation is not justified. We, however, found that patients who received epidural midazolam were able to initiate ambulation much earlier than the other group. This finding has not been previously addressed and we reckon that if a definite cause-effect relationship can be established, this one possible advantage of epidural midazolam is significant enough to recommend its routine use.

Conclusion

Midazolam when administered through the epidural

route in a small dose is safe. It does not have significant anti-nociceptive effect, but it may improve post-operative nausea, vomiting, and may lead to earlier ambulation without affecting a patient's vitals, conscious status, lower extremity power or sensations. A larger sample size is recommended to further improve the significance of these findings.

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