OPIOID SPARING EFFECT OF POST-INDUCTION INTRAMUSCULAR MIDAZOLAM FOLLOWING MYOMECTOMY

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Abstract

Background: Adequate post-operative pain control is essential for smooth recovery after surgery. This study assessed the opioid-sparing effect of immediate post-induction intramuscular midazolam in patients who underwent myomectomy under general anesthesia.

Methods: This is a randomized double-blinded controlled study of sixty ASA I and II female patients allocated into three groups. Group A received intramuscular midazolam 0.1mg/kg, group B received intramuscular diclofenac 75mg while group C had a placebo following induction of anesthesia. All patients had morphine 0.1mg/kg for intraoperative analgesia before skin incision. Pain scores were compared at recovery, then at 1st, 2nd, 4th and 8th post-operative hours. In addition, the total opioid consumption over the first 24 hours postoperatively was compared between the three groups.

Results: The pain scores at the end of surgery, 1st and 2nd hours were comparable in the 3 groups; however there was statistically significant difference at the 4th hour postoperatively (p = 0.0001), with lowest pain scores in the midazolam and diclofenac groups (3.70 ± 0.66 and 3.80 ± 1.01 respectively) compared to the placebo group (4.75 ± 0.79). The total additional opioid (pentazocine) consumption in first 24 hour after surgery was significantly reduced in the midazolam group (105.00 ± 15.39 mg) compared to diclofenac and placebo groups (112.50 ± 13.33 mg, and 121.50 ± 18.14 mg respectively, p = 0.007).

Conclusion: Post induction intramuscular Midazolam at 0.1mg/kg appears to have a better opioid sparing effect compared to intramuscular diclofenac 75mg in the early postoperative period following myomectomy done under general anesthesia.

Keywords: Midazolam, Adjuvant, Post-induction, Post-operative pain, Myomectomy.

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Introduction

Pain has been defined as "an unpleasant sensory and emotional experience, associated with actual or potential tissue damage or described in terms of such damage" by the International Association for the Study of Pain.[1] Pain is what the sufferer says it is, and it is present when, and where he/she says it is.[1] Poorly managed pain results in varying multisystemic complications including emotional and physical suffering, sleep disturbance, cough suppression and atelectasis, hypertension and arrhythmias, impaired gastrointestinal motility, delayed mobilization and increased sympathetic activities.[2] Besides concerns of prolonged recovery and rehabilitation, pain still ranks among the highest patients' and physicians' concerns for undesirable surgical outcomes.[3]

Though, opioids form the central core of pharmacological agents used in the management of acute post-operative pain, multimodal approach to pain management with medications acting through different mechanisms has been established to be superior to mono-therapy. Several drugs including analgesics and non-analgesics have been used as adjuvants to opioids for their opioid-sparing effect. Improved quality of analgesia and reduced opioid side-effects have been associated with the use of these medications.[3,8-10] Drugs that have been employed as adjuvants include anticonvulsants, anxiolytics, antidepressants, corticosteroids, alpha-2 adrenergic agonists and N-methyl-D-aspartate (NMDA) receptor antagonists.

Perioperative anxiety has been correlated with increased postoperative pain, however the role(s) of perioperative benzodiazepine therapy on postoperative pain still largely remains unclear.[3,4] Midazolam, a short acting water soluble benzodiazepine, is used routinely for sedation, premedication and induction of anesthesia. It has also been shown to increase the threshold to pain on intrathecal administration.[11] Midazolam has been reported by few clinicians[9,12] to possess some opioid-sparing effects in the management of pain. The efficacy of intramuscular midazolam as an adjuvant to opioids in acute post-operative pain management in adult males who had elective inguinal herniorrhaphy under general anesthesia has been reported.[9] There are also few contrary opinions against this claim.[13] However, there is paucity of literature to verify these divergent results.

This study was conducted to determine the opioid sparing effect of intramuscular midazolam during postoperative period when used as an adjuvant to morphine as intraoperative analgesic in patients undergoing myomectomy under general anesthesia. A secondary outcome was to evaluate the side effects of intramuscular midazolam in this group of patients.

Methods

This is a prospective placebo-controlled study of adult female aged 18 - 60 years, American Society of Anesthesiologists (ASA) physical status I or II who underwent elective myomectomy under general anesthesia. The exclusion criteria were refusal to give consent for the study, ASA physical status greater than II, history of allergy to midazolam or benzodiazepines, morbid obesity, chronic opioid use, history of allergy to any opioid or NSAIDs, poorly controlled chronic medical illnesses, and conversion of procedure to hysterectomy. Ethical approval was obtained from the Ethics and Research Board of the hospital, and written informed consent was obtained from all patients who satisfied the inclusion criteria.

Randomization was performed by the anesthestist responsible for preparation of the drugs, while the attending anesthestist responsible for drugs administration was blinded to patient's group. The lead investigator, also blinded to patients' grouping evaluated all the patients after drug administration. The patients were equally blinded to their grouping. Group A patients had intramuscular midazolam at a dose of 0.1mg/kg diluted to 3ml with normal saline immediately after induction of anesthesia, while group B patients received 75mg of diclofenac (25mg per ml preparation) intramuscularly after induction. Group C (Placebo) received 3ml of normal saline. All participants were assessed preoperatively, and educated on the use of Numerical Rating Scale (NRS).

In the operating room, the baseline vital signs including pulse rate (PR), non-invasive blood pressure (NIBP), mean arterial pressure (MAP), respiratory rate (RR), and peripheral oxygen saturation (SpO2) were

measured with the Dash 4000 multi-parameter monitor (GE Healthcare, United Kingdom, 2003) and recorded. Intravenous access was secured with a size 18G cannula; and maintenance fluid instituted with 0.9% saline. All patients were pre-oxygenated with 100% oxygen, and pre-medicated with 0.2mg glycopyrolate. Following intravenous induction with propofol 2mg/kg, the allotted injection was administered into the deltoid muscle with a 23G hypodermic needle by the attending anesthestist. Either a size 7.5mm or 8mm cuffed endotracheal tube was inserted following adequate airway relaxation achieved with 1.5mg/kg of suxamethonium. Anesthesia was maintained with 0.8-1.2% isoflurane in oxygen-air mixture administered with sodalime absorber system. Electronic monitoring continued intraoperatively. Intravenous morphine 0.1mg/kg was administered before skin incision for intraoperative analgesia. Muscle relaxation was achieved with pancuronium 0.1mg/kg, and maintained with top-up doses as required. At the end of the surgery, the inhalational agent was discontinued, and residual neuromuscular blockade was reversed with neostigmine 0.05mg/kg premixed with 0.02mg/kg atropine. The patients were extubated awake, and given 100% oxygen by facemask at a flow rate of 3-4L/min after achieving a dry airway. After satisfactory recovery, they were transferred to the recovery room and observed for an hour. Type of skin incision, time and duration of surgery, vital signs on arrival to the recovery room (Time 0), and 1st hour after surgery were recorded. Post-operative analgesia was provided with intravenous pentazocine 30mg 6 hourly and intravenous paracetamol 1g 8 hourly according to the departmental protocol. Pain was assessed at 0, 1st, 2nd, 4th and 8th hours postoperatively. Breakthrough pain was managed using pentazocine 30mg. Additional analgesia was given at any point where NRS was greater than 4. The total opioid consumption over the first 24 hours was recorded. Side effects of opioids such as post-operative nausea and vomiting, pruritus and respiratory depression were sought for and recorded.

Fig. 1
Flow diagram of patients from evaluation to completion

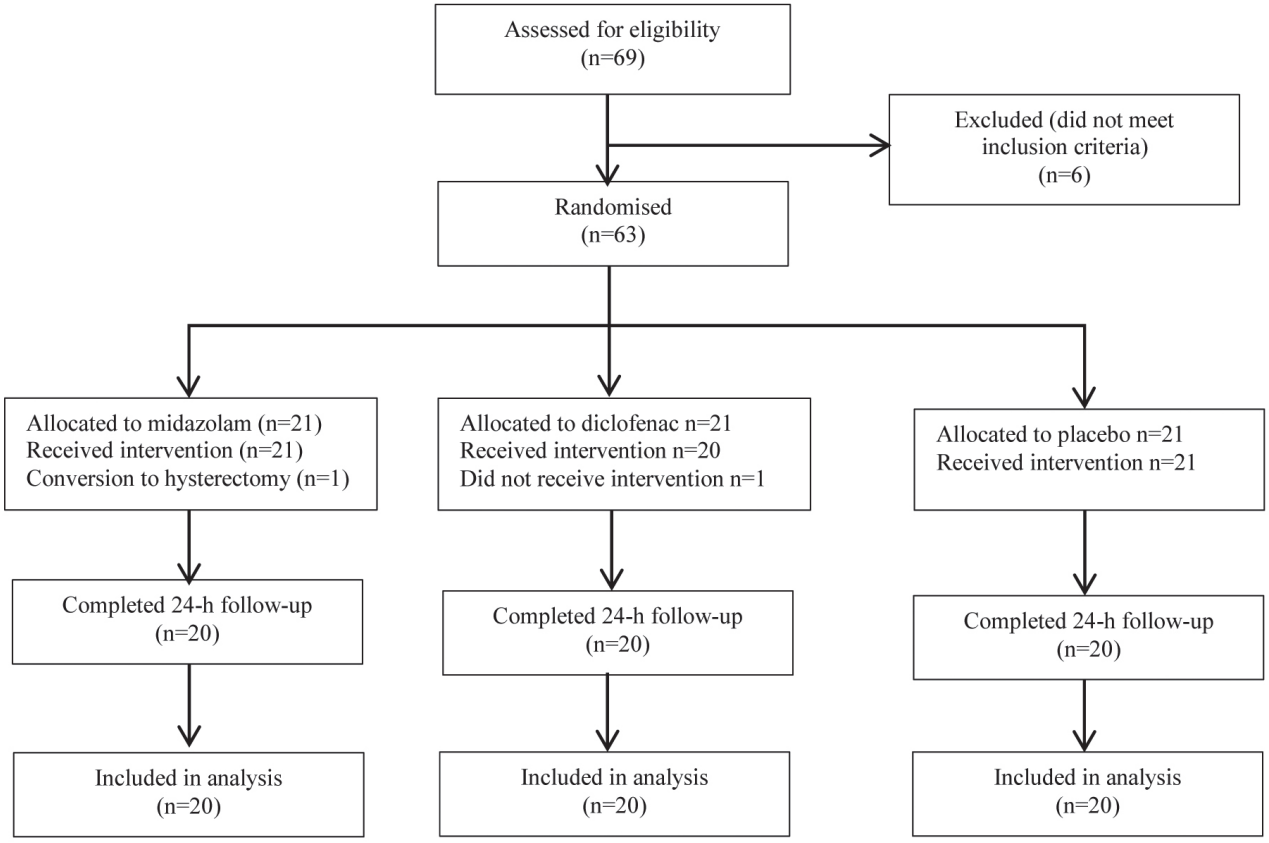


Table 1

Patients demographics (Mean ± SD)

Demographic characteristics	**Group A (n=20)**	**Group B (n=20)**	**Group C (n=20)**	**p - value**
Age (yrs)	35.70 ± 4.73	33.95 ± 5.14	37.75 ± 6.89	0.114
BMI (kg/m^2)	25.50 ± 4.07	24.85 ± 3.23	25.00 ± 3.43	0.648
Duration of surgery (minutes)	166 ± 49	133 ± 53	159 ± 52	0.107

SD - Standard Deviation

Table 2

Comparison of Pain scores between groups A and B (Mean ± Standard deviation)

Pain scores	**Group A (n = 20)**	**Group B (n = 20)**	*p* - value
NRS^{end}	3.75 ± 1.12	4.20 ± 1.24	0.222
NRS1st	4.05 ± 0.61	4.40 ± 1.23	0.415
NRS2nd	3.70 ± 0.66	3.95 ± 0.69	0.209
NRS4th	3.70 ± 0.66	3.80 ± 1.01	0.090
NRS8th	3.80 ± 0.41	3.75 ± 0.44	0.371

SD - Standard Deviation

NRS^{end} - Mean Pain score at the end of surgery, NRS^{1st} - Mean Pain score at the first hour postoperatively, NRS^{2nd} - Mean Pain score at the second hour postoperatively, NRS^{4th} - Mean Pain score at the fourth hour postoperatively, NRS^{8th} - Mean Pain score at the eighth hour postoperatively.

Table 3

Comparison of Pain scores at different time intervals between groups A and C (Mean ± SD)

Pain scores	**Group A (n = 20)**	**Group C (n = 20)**	**p - value**
NRS^{end}	3.75±1.12	4.40±1.19	0.242
NRS1st	4.05±0.61	4.25±0.72	0.357
NRS2nd	3.70±0.66	4.10±0.79	0.109
NRS4th	3.70±0.66	4.75±0.79	0.001
NRS8th	3.80±0.41	3.95±0.50	0.161

SD - Standard Deviation

NRS^{end} - Mean Pain score at the end of surgery, NRS^{1st} - Mean Pain score at the first hour postoperatively, NRS^{2nd} - Mean Pain score at the second hour postoperatively, NRS^{4th} - Mean Pain score at the fourth hour postoperatively, NRS^{8th} - Mean Pain score at the eighth hour postoperatively.

Table 4

Comparison of the mean of total Opioid consumption in 24 hours (Mean ± SD)

Opioid	**Group A (n=20)**	**Group B (n=20)**	**Group C (n=20)**	**P-value**
Morphine	6.30 ± 1.03	6.60 ± 1.05	6.10 ± 0.95	0.298
Pentazocine	105.00 ± 15.39	112.50 ± 13.33	121.50 ± 18.14	0.007
Amount of Pentazocine spared (mg)	16.5	9.0	0.0	-

SD - Standard Deviation

Statistical analysis

The sample size was determined using the Snedecor-Cochran equation for comparing means of independent groups. n = 1+ 2C (s/d)2 where: n = sample size per group; s = standard deviation (0.45) extrapolated from the previous study by Akhlaghi5; d = minimum difference in mean to be detected (0.5) based on previous works9,14; and c (10.51) is a constant derived from the probability of type 1 and type 2 errors. n = 1 + 2 x 10.51(0.45/0.5)2 = 18.03. i.e. 18 patients in each group. The sample size was increased by 10% to provide for attrition (18 + 1.8 = 19.8). A total of 69 patients were recruited for the study, but only 60 who completed the study were included in the final analysis as shown in figure 1.

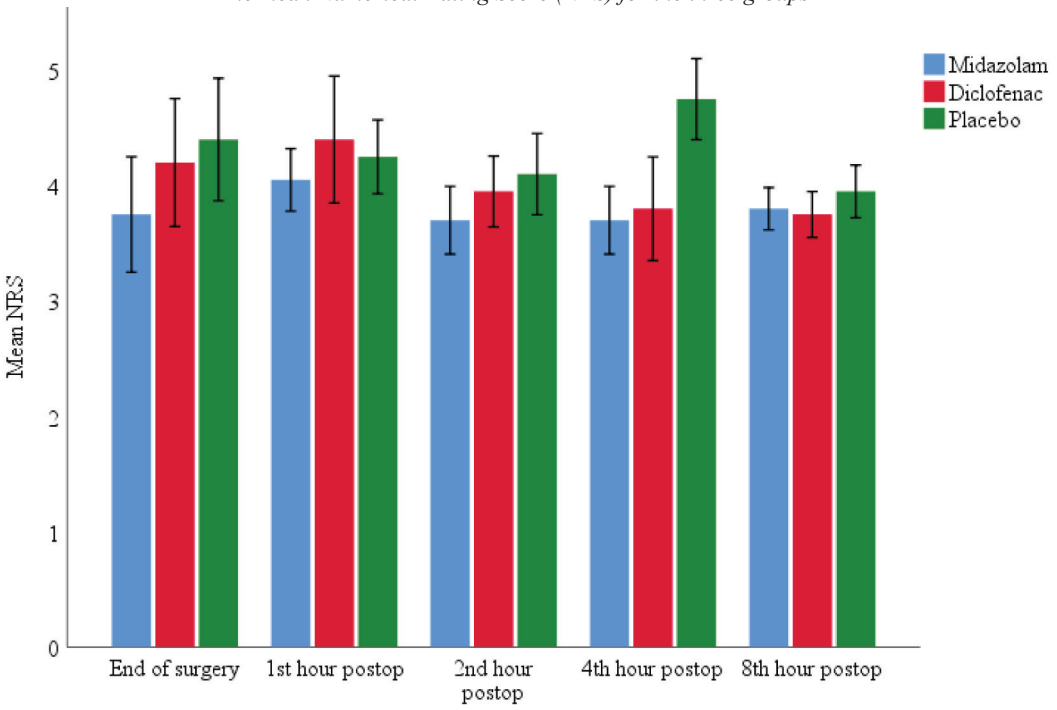
Data was analysed on IBM Statistical Package for Social Sciences (SPSS) 22. Intergroup comparisons of parametric variables were performed using Analysis of Variance (ANOVA) or student t-test as appropriate. Chi-square (X^2) analysis was used for non-parametric variables. For all statistical analyses, $p < 0.05$ was accepted as significant.

Results

The demographic characteristics of the three groups were similar (Table 1). The mean pain scores were comparable statistically between the midazolam and diclofenac groups throughout the period of study (Table 2). However, the midazolam group had a significantly lower mean pain score compared to the placebo group at the 4th postoperative hour ($p = 0.001$) (Table 3). The mean pain scores across the three groups was found to be lowest in midazolam group compared to the diclofenac and placebo groups throughout the study period except at the 8th hour when diclofenac group had a lower mean score as shown in Figure 2. The difference in total pentazocine consumption within the first 24 hours after surgery was found to be statistically significant ($p = 0.007$). The overall pentazocine consumption was significantly lower in the midazolam group compared to the diclofenac and placebo groups (105.00 ± 15.39 mg versus 112.50 ± 13.33mg and 121.50 ± 18.14 mg respectively, $p = 0.007$). The absolute amount of pentazocine spared in the midazolam group was 16.5mg. In diclofenac group, it was 9.0mg (Table 4).

Fig. 2

The mean Numerical Rating Score (NRS) for the three groups



NB: Error Bars: 95% Confidence Interval **p = 0.0001 at 4th postoperative hour*

The placebo group had significantly higher mean pulse rate compared to midazolam and diclofenac groups at the 1st, 2nd, 4th and 8th postoperative hours ($p < 0.05$) (Figure 3). However, the mean systolic and diastolic blood pressures across the three groups were comparable except at the 1st hour and the 4th hour post operation respectively (Figures 4 and 5).

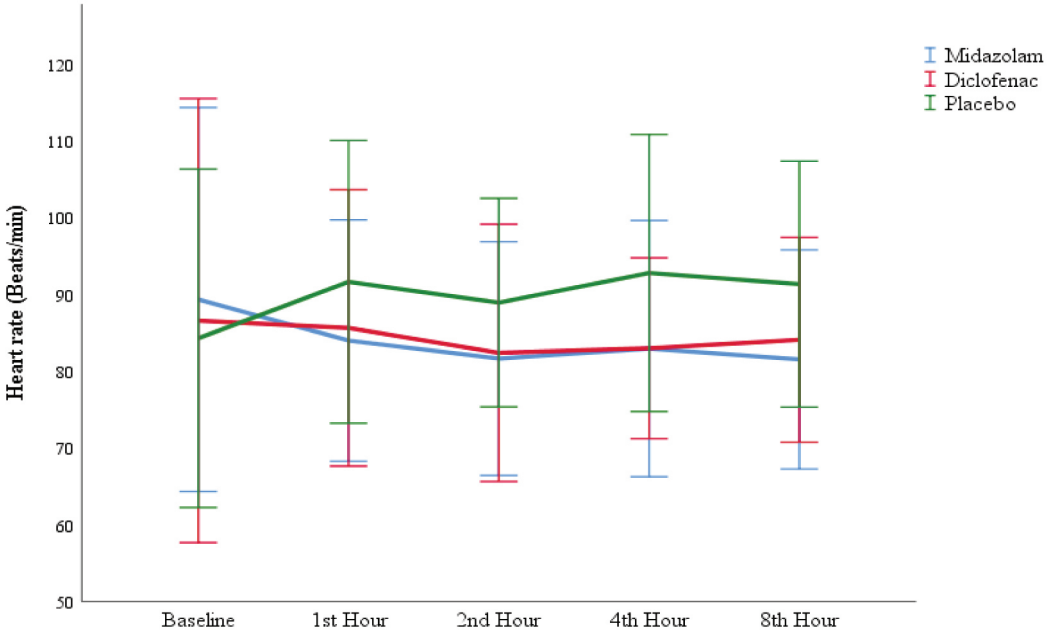
Postoperative mild sedation was observed in ten patients (16.6%) at the post anesthesia care unit immediately after surgery. Seven of those (11.7%) were in midazolam group, 2 (3.3%) in diclofenac group and 1 patient (1.7%) in placebo group. The difference was statistically significant across the groups ($p = 0.024$). A single patient (1.7%) in diclofenac group reported pruritus. No other side effects were noticed.

Discussion

The results of this study suggest that intramuscular midazolam administered immediately after induction of general anesthesia at a dose of 0.1mg/kg was an effective adjuvant to opioid analgesic comparable to intramuscular 75mg diclofenac. It provided a significantly better pain score compared to placebo in the immediate postoperative period particularly at the 4th hour postoperative hour. This finding is in tandem with earlier report by Akhlaghi and Rajaei[9] who showed that intramuscular midazolam administered immediately after induction of anesthesia can reduce postoperative pain intensity particularly during the first 3 hours following a minor surgery. It is also in agreement with the report of Artru[14] who reported that the addition of midazolam as an adjunct to opioids is helpful in opioid dose reduction without compromising quality of analgesia.

Although, Akhlaghi and Rajaei[9] reported statistically significant reduction in pain scores at the first and second hours after surgery, statistically significant reduction in the mean pain score of the midazolam group was observed only at the 4th hour in our patients. This difference could be related to the type (myomectomy) and extensiveness of the procedures in the current study compared to their study population (herniorrhaphy). The results of this study also suggest that midazolam may be a suitable adjunct to opioids for patients with contraindications to non-steroidal anti-inflammatory drugs (NSAIDs) like diclofenac during the immediate postoperative period. The mean numerical pain scores of patients in midazolam and diclofenac groups were found to be

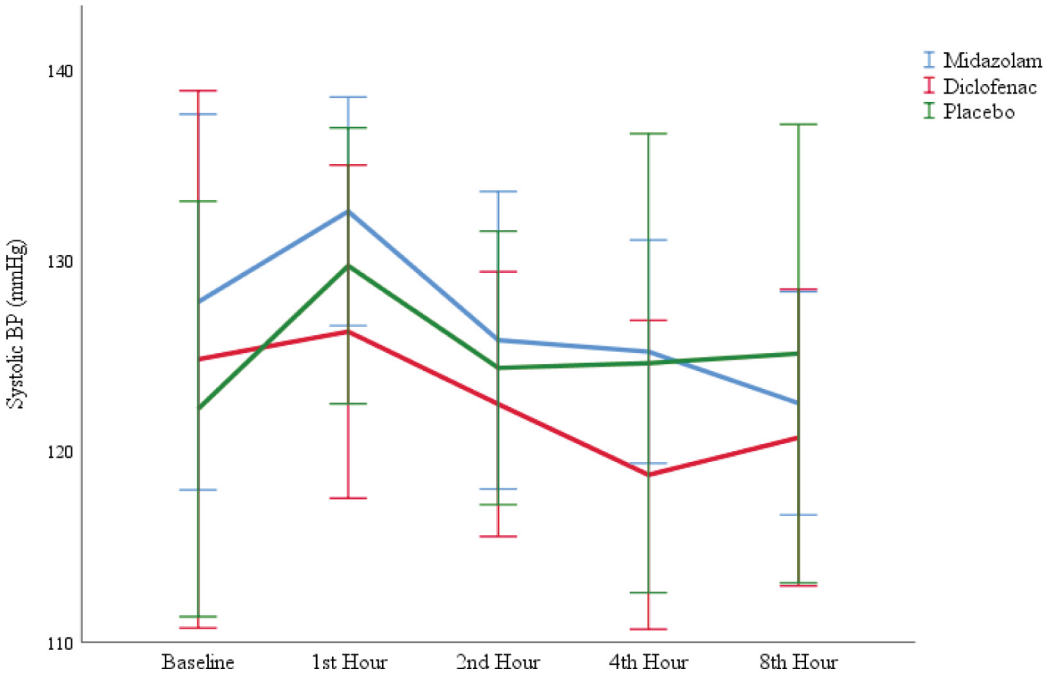
Fig. 3
Mean pulse rate of all groups



*NB: *p = 0.019, 0.006, 0.0001, and 0.0001 at the 1st, 2nd, 4th, and 8th hour post operation respectively.*

Fig. 4

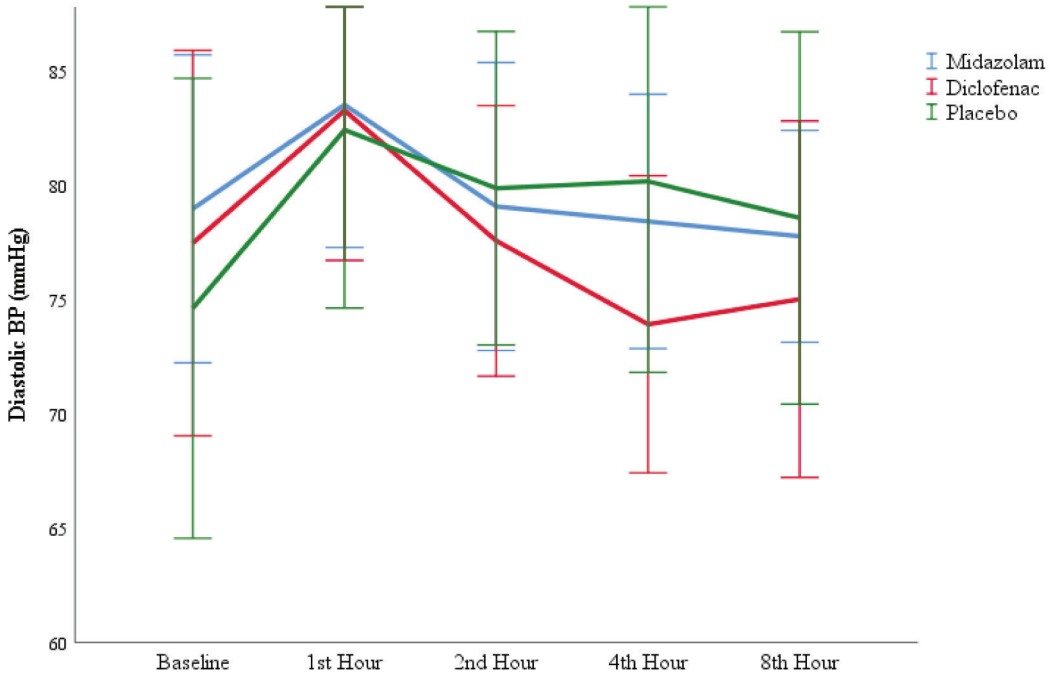
Mean systolic blood pressure of all groups



*NB: *p = 0.033 at the 1st hour post operation.*

Fig. 5

Mean diastolic blood pressure of all groups



*NB: *p = 0.017 at the 4th hour post operation.*

comparable. Diclofenac has long been established as an effective adjunct to opioids in pain management, and in some instances as a sole analgesic following total abdominal hysterectomy.[20] However, a superior opioid sparing effect with intramuscular midazolam compared to intramuscular diclofenac was observed. The total 24 hours pentazocine consumption was least in midazolam group with a mean total of 16.5mg pentazocine spared compared to a mean total of 9mg observed in diclofenac group. It is worthy to note that midazolam administered through different routes for various procedures has been reported to effectively reduce analgesic requirements in the first 24 hours after surgeries in several previous studies.[18,21,35]

The results from the present study also suggest significant cardiovascular benefit. The lowest mean pulse rate trend recorded in midazolam group compared to diclofenac and placebo groups. This may be an important factor in the management of cardiovascular high risk patients who require better stability in pulse rate. This beneficial effect of midazolam on hemodynamic stability of patients has been previously reported by others.[22,23] However, significant reduction in blood pressure was not observed in this study.

Sedation was the main complication observed in this study. Seventy percent of the patients who had sedation in the current study were in midazolam group, and this was found to be statistically significant. Klain *et. al.*[24] noted that sedation was the most common complication in the first hour after surgery similar to what we observed in this study. This risk of postoperative sedation is understandably higher in patients premedicated with long-acting benzodiazepine as reported by Klain *et. al.*[24] Only one patient (1.7%) in diclofenac group had pruritus. Though this finding was not statistically significant, Makarem *et. al.*[25] recently reported that intravenous midazolam administered at a dose of 0.03mg/kg bolus then followed by 0.02mg/kg/h infusion effectively prevented intrathecal sufentanil-induced pruritus when compared to propofol in patients who had spinal anesthesia.

Conclusion

The results of this study suggest that intramuscular midazolam given preoperatively at a dose of 0.1mg/kg is an effective analgesic adjuvant comparable to 75mg of intramuscular diclofenac in patients undergoing myomectomy under general anesthesia. However, this study was conducted on patients for elective surgery, and it may be difficult to extrapolate these results in emergency scenarios, obese patients and the elderly.

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Conflict of Interest: The authors declare that they do not have any potential conflicts of interest.

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References

1. Merskey H. Pain terms: A list with definitions and usage, IASP subcommittee on taxonomy. Pain. 1979; 6: 249-52.
2. Racz GB, Noe CE, Sivrikaya GU. Pain management - current issues and opinions. Multimodal analgesia for postoperative pain management. 1st Ed. Croatia. InTech Open science 2011; 177-202.
3. Chandrakantan A, Glass PS. Multimodal therapies for postoperative nausea and vomiting, and pain. Br J Anaesth. 2011; 107: 27-40.
4. Bauer KP, Dom PM, Ramirez AM, O'Flaherty JE. Perioperative intravenous midazolam: Benefit beyond anxiolysis. J Clin Anesth. 2012; 16: 177-83.
5. Ndububa VI. Uterine fibroids: Experience with 100 myomectomies in Orlu, South East Nigeria. Port Harcourt Med J. 2016; 10: 124-9.
6. Okogbo FO, Ezechi OC, Loto OM, Ezeobi PM. Uterine leiomyomata in South Western Nigeria: A clinical study of presentations and management outcome. Afr Health Sci. 2011; 11: 271-8.
7. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg.1993; 77: 1048-56.
8. Caumo W., Hidalgo M. P. L, Schmidt A. P., Iwamoto C. W. Adamatti L. C, Bergmann J. Ferreira M. B. Effect of pre-operative anxiolysis on postoperative pain response in patients undergoing total abdominal hysterectomy. Anesthesia. 2002; 57: 740-6.
9. Akhlaghi M, Rajaei M. The effect of intramuscular midazolam on postoperative pain resulting from herniorraphy: J Med Sci 2008; 8: 302-5.
10. Karbasfrushan A, Farhadi K, Amin-Saman J, Bazargan H, Ahmadi A. Effect of intrathecal midazolam in the severity of pain in caesarean section: A randomised controlled trial. Iran Red Crescent Med J. 2012; 14: 276-82.
11. Nishiyama T. Analgesic effects of systemic midazolam: comparison with intrathecal administration. Can J Anaesth. 2006; 53:1004-9.
12. Suwalka U, Patel J, Mehta K. Postoperative analgesia with intrathecal midazolam in caesarean section deliveries. IJRRMS. 2012; 2: 1-4.
13. Majidi A, Dinpanah H, Ashoori S, Motamed H, Tabatabaey A. Comparison of Morphine-midazolam versus morphine injection for pain relief in patients with limb fractures - a clinical trial. TJTES. 2015; 21: 22-6.
14. Artru A.A. Midazolam Potentiates The Analgesic Effect Of Morphine In Patients With Postoperative Pain. Clin J Pain. 1986; 2: 93-100.
15. Ogboli-Nwasor E, Sule ST, Yusufu LM. Pattern of postoperative pain management among adult surgical patients in a low-resource setting. J Pain Res. 2012; 5: 117-20.
16. Batra YK, Jain K, Chari P, Dhillon MS, Shaheen B, Reddy GM. Addition of intrathecal midazolam to bupivacaine produces better post-operative analgesia without prolonging recovery. Int J Clin Pharmacol Ther. 1999; 37: 519-23.
17. Buvanendran A, Jacqueline F, Karishma AP, Alexandra DG, Mario M, Jeffrey SK. The Incidence and Severity of Postoperative Pain following Inpatient Surgery. Pain Med. 2015; 16: 2277-83.
18. Masigati HG, Chilonga KS. Postoperative pain management outcomes among adults treated at a tertiary hospital in Moshi, Tanzania. Tanzania Journal of Health Research. 2014; 16: 1-10.
19. Hofer CK, Zollinger A, Buchi S, Klaghofer R, Serafino D, Buhlmann S, Buddeberg C, Pasch T, Spahn DR. Patient well-being after general anesthesia: a prospective, randomized, controlled multi-centre trial comparing intravenous and inhalation anesthesia. Br J Anaesth. 2003; 91: 631-7.
20. Anirban P, Jihuma B, Purnava M, Poushali S, Shyamal D, Shymasshis D. Diclofenac is more effective for postoperative analgesia in patients undergoing lower abdominal gynaecological surgeries: A comparative study. Anesth Essays Res. 2014; 8: 192-6.
21. Adetoye AO, Adenekan AT, Faponle AF, Sowande AO, Owojuyigbe AM. Caudal bupivacaine and midazolam versus bupivacaine alone for pain relief in paediatric ambulatory groin surgeries. PACCJ. 2017; 5: 95-102.
22. Win NN, Kohase H, Yoshikawa F, Wakita R, Takahashi M, Kondo N, Ushito D, Umino M. Haemodynamic changes and heart rate variability during midazolam-propofol co-induction. Anesthesia. 2007; 62: 561-8.
23. Kim JD, Kim JW, Kung HC, Kang JH, Shin HY, Kim DS, Ryu JS, Kim KH. Hemodynamic Effects of Co-administration of Midazolam during Anesthesia Induction with Propofol and Remifentanil in Hypertensive Patients. KMJ. 2017; 32: 36-46.
24. Klain ZN, Sevarino FB, Rinder C, Pincus S, Alexander GM, Ivy M, Heninger G. Preoperative anxiolysis and postoperative recovery in women undergoing abdominal hysterectomy. Anesthesiology. 2001; 94: 415-22.
25. Makarem J, Mireskandari, SM, Jafarzadeh A, Nikoukar LR, Aghaii S. Intravenous Midazolam as More Effective Than Propofol for Preventing Pruritus After Intrathecal Sufentanil in Surgical Patients: A Randomized Blinded Trial. Anesth Pain Med. 2017; 7: 1-9.