Original Research Article

Intrathecal buprenorphine as an adjuvant to 0.5% bupivacaine in vaginal hysterectomy

Jagadish Chandra Mishra[1*], Pradip Kumar Maharana[2]

[1]Associate Professor, [2]Assistant Professor
Kalinga Institute of Medical Sciences (KIMS), KIIT University, Bhubaneswar, Odisha, India
[*]Corresponding author email: **mishrajccb@gmail.com**

International Archives of Integrated Medicine, Vol. 4, Issue 11, November, 2017.

Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 12-10-2017 **Accepted on:**19-10-2017
Source of support: Nil **Conflict of interest:** None declared.
How to cite this article: Jagadish Chandra Mishra, Pradip Kumar Maharana. Intrathecal buprenorphine as an adjuvant to 0.5% bupivacaine in vaginal hysterectomy. IAIM, 2017; 4(11): 99-105.

Abstract

Background: One of the most suitable modality of anaesthesia for lower abdominal surgeries is spinal anaesthesia. The relatively short duration of action of local anaesthetics necessitates the supplementation of local anaesthetics with adjuvants which help to reduce the dose of local anaesthetic, minimize side effects and prolong the duration of anaesthesia at a relatively lesser cost to the patient.

Aim: To evaluate the characteristics of subarachnoid block, the postoperative analgesia and side effects of intrathecal buprenorphine 150 µg when used as adjuvant to 0.5% bupivacaine, for vaginal hysterectomy.

Materials and methods: After approval from the hospital ethical committee and informed consent from the patients a prospective pilot study was undertaken to evaluate the efficacy of intrathecal buprenorphine when used as an adjuvant to 0.5% bupivacaine. All patients belonged to American Society of Anesthesiologist's Physical status I and II and aged between 33 and 60 years. Patients were allocated into two groups. Group A were to receive 0.5% bupivacaine 2.5 mL. Group B were to receive 0.5% bupivacaine 2.5mL with buprenorphine 150 µg. It was observed that most of group A patients had to receive general anaesthesia in addition to subarachnoid block due to inadequate pain relief. The data of group B patients were analysed.

Results: Of the 49 patients analyzed, 13 patients had pain free interval which lasted more than 24 hours. Twelve patients who received a single dose of diclofenac 75 mg intravenously before the onset of pain had a pain free interval which lasted more than 24 hours. The average duration of analgesia of 37 patients was 1027 minutes ± 706.662.

Conclusions: A single dose of intrathecal buprenorphine 150 µg added to bupivacaine may provide analgesia for a significant length of time in patients who have undergone vaginal hysterectomy without significant side-effects.

Key words

Intrathecal, Buprenorphine, Vaginal hysterectomy, Spinal anaesthesia, Postoperative pain.

Introduction

Hysterectomy is one of the most frequently performed surgical procedures in the gynaecological department in our institution. Hysterectomy when performed vaginally enables more patient comfort, less morbidity, early ambulation and shorter hospital stay at a lesser cost [1].

In our centre vaginal hysterectomy patients are generally discharged within 4 days to 8 days. Lower abdominal surgeries are most commonly performed under spinal anaesthesia. The relatively short duration of action of local anaesthetics necessitates supplementation of local anaesthetics with adjuvants. This reduces the dose of local anaesthetic, minimizes side effects and prolongs the duration of anaesthesia at a relatively lesser cost to the patient [2, 3].

Buprenorphine is a mixed agonist-antagonist narcotic with affinity at both mu and kappa opiate receptors [4, 5]. It is lipophilic, long acting and 25 times more potent than morphine. It has a ceiling effect on the respiratory depression but not on analgesic effect in humans when given intravenous Its cost-effectiveness, easy availability and low abuse potential makes it an attractive option to be used as an adjuvant for spinal anesthesia [5-8].

The aim of the study was to evaluate the characteristics of subarachnoid block, the duration of pain free period and side effects of intrathecal buprenorphine 150 µg when used as an adjuvant to 0.5% bupivacaine for vaginal hysterectomy.

Materials and methods

After approval from the hospital ethical committee and informed consent from the patients a prospective pilot study was undertaken. Sixty patients belonging to American Society of Anesthesiologist's Physical status I and II undergoing vaginal hysterectomy under spinal anaesthesia were included for the study. Patients with bleeding disorders, on anticoagulants, cardiac disease, heart block, local sepsis and hypersensitivity to study drug were excluded from the study. A sample size of 30 in each group was calculated. Patients were allocated into two groups. Group A were to receive 0.5% bupivacaine 2.5 mL. Group B were to receive 0.5% bupivacaine 2.5mL with buprenorphine 150 µg.

All patients were pre-medicated with tablet alprazolam 0.25 or 0.5 mg night before surgery and 2 hours prior to the surgery. Subarachnoid block was performed with 25/26 G spinal needle at L_{3-4} or L_{4-5} interspace. Intraoperative monitoring was done with non-invasive blood pressure (NIBP), pulse oximeter, ECG (electrocardigram). All patients received oxygen supplementation with a face mask. Sensory testing was done by pin prick. Motor block was assessed using modified Bromage scale [9]; Bromage 0-patient is able to move hip, knee, ankle; Bromage 1-not able to move hip but able to move knee and ankle; Bromage 2-not able to move hip and knee, but able to move ankle; Bromage 3-not able to move hip, knee and ankle. The time taken to reach modified Bromage 3 was taken as complete motor block. Sedation was assessed by Ramsay sedation score [10]; 1-Anxious, agitated; 2-Co-operative, oriented and tranquil; 3-Responding to commands; 4-Brisk response to glabellar tap; 5-Sluggish response to glabellar tap; 6- no response. Side effects such as

respiratory depression [respiratory rate (RR) <8-10/min)], oxygen desaturation, nausea, vomiting, pruritus, postdural puncture headache and shivering were assessed. Diclofenac 75 mg intravenous (I.V) was administered as rescue analgesic, when patient demanded analgesics.

HR< 50 bpm was treated with atropine 0.5 mg IV and hypotension (fall in systolic blood pressure more than 25% from the baseline) was treated with ephedrine 6 mg IV. Nausea and vomiting was managed with ondensetron 4 mg IV. Grade 3/4 shivering was treated with pethidine 0.5mg/kg IV.

It was observed that most of group A patients had to receive general anaesthesia in addition to subarachnoid block due to inadequate pain relief. The data of group B patients were analysed.

Data was expressed as mean ± standard deviation (SD) or as absolute values. Using repeated measure ANOVA by Greenhouse Geisser method, the heart rate (HR), mean arterial blood pressure (MAP), respiratory rate (RR) at every interval were compared with the basal values.

Results

A total of 49 patients who were operated for vaginal hysterectomy were included in the study. Average of parameters such as age, weight and surgical time was calculated and the SD estimated. The average age was 44.55 ±6.652 years, the average weight was 57.94 ± 8.661 kg and the average surgical time was 112.59 ±36.501 min.

Of the 49 analyzed, 12 patients, in addition to the study drug also received diclofenac 75 mg intravenously before the onset of pain. In these patients duration of analgesia lasted for more than 24 hours but could not be included when assessing the duration of analgesia provided by the study drug.

The average duration of pain free period of 37 patients was 1027 minutes ± 706.662. There was a fair degree of variability in the duration of analgesia between the patients receiving the drug. It was seen that the analgesia lasted from a least of 3 hours in 1 patient, to a maximum of 48 hours in 2 patients. 13 patients had pain free interval which lasted more than 24 hours.

The characteristics of spinal anaesthesia was as per **Table - 1**.

The average basal HR and the mean HR, at regular intervals was recorded and expressed as mean ± SD (**Table – 2**). The HR at every interval was compared with the basal HR and the difference was found to be statistically significant (**Table – 3**). The criterion for statistical significance for all analyses was set at P<0.01. Atropine 0.6 mg I.V was given in 8 patients. Occasional ectopics were observed in 3 patients.

Table – 1: Characteristics of spinal block. (SD=standard deviation)

	Mean±SD
Time taken for maximum motor block (min)	9.12±3.908
Time taken to achieve sensory T10 (min)	3.02±1.436
Duration of analgesia achieved (min)	1027.73±706.662

The average basal MAP and the MAP every 5 minutes for the first 30 minutes and subsequently every 15 minutes till the end of the surgery was estimated. Data was expressed as mean ±SD (**Table – 2**). The MAP at every interval was compared with the basal MAP and the difference was found to be statistically significant (**Table – 3**).

The average basal RR and the mean RR at regular intervals were recorded and expressed as mean ±SD (**Table – 2**). The mean RR at every

interval was compared with the basal RR and the difference was found to be statistically significant (**Table – 3**).

Among the side-effects (**Table – 4**), the incidence of vomiting was 26.53 % although the incidence of nausea was 32.65%. The incidence of the most dreaded complication i.e. respiratory depression was quite low, with only one patient developing a RR of 8 and another with RR of 10 which was self-limiting, needed only monitoring. The average sedation score was found to be 2.20 ±0.539.

Table – 2: Average heart rate, mean arterial pressure, respiratory rate. (HR=heart rate, MAP=mean arterial pressure, RR=respiratory rate)

Minutes	Mean HR±SD	MAP (mm Hg) ±SD	Mean RR±SD
basal	86.73± 14.741	107.73±13.788	19.29±3.690
5	84.36±16.552	96.71±12.403	18.60±3.540
10	77.29±15.521	89.90±13.976	17.98±3.733
15	72.04±13.389	86.85±13.134	16.98±3.199
20	70.40±12.101	85.48±12.213	16.65±2.950
25	70.16±11.730	82.67±12.665	16.31±3.005
30	68.78±11.239	83.38±12.068	16.10±2.769
45	67.64±9.953	82.65±10.299	15.65±3.179
60	65.58±10.046	81.26±116.273	15.05±2.800
75	66.44±10.759	85.51±9.420	14.95±2.772
90	66.03±9.541	86.10±10.465	14.67±2.679

Table – 3: HR, MAP, RR compared to the basal (P<0.01 was statistically significant)

	P (HR)	P (MAP)	P (Mean RR)
Level 2 vs.Level 1	0.095	0.000	0.002
Level 3 vs Level 1	0.000	0.000	0.002
Level 4 vs Level 1	0.000	0.000	0.000
Level 5 vs Level 1	0.000	0.000	0.000
Level 6 vs Level 1	0.000	0.000	0.000
Level 7 vs Level 1	0.000	0.000	0.000
Level 8 vs Level 1	0.000	0.000	0.000
Level 9 vs Level 1	0.000	0.000	0.000
Level 10 vs Level 1	0.000	0.000	0.000
Level 11 vs Level 1	0.000	0.000	0.000

Table – 4: Side effects. (n=number of patients)

	n=49 (%)
Nausea	16 (32.65)
Vomiting	13 (26.53)
Pruritus	4 (8.16)
Headache	2 (4.08)
Shivering	5 (10.02)
RR <8	2 (4.08)

Discussion

Buprenorphine when used as an adjuvant prolonged the pain free period in our study. High lipid solubility, high affinity for opiate receptors and slow dissociation constant of drug receptor complex makes buprenorphine a good choice when used intrathecally [11, 12]. Buprenorphine produces longer duration of analgesia than reported for other lipophilic agents [13-15].

Data from the present study of 37 patients, showed that the average pain free period obtained with intrathecal buprenorphine was 1027 min ± 706.662. In a study by Ipe *et al* the addition of buprenorphine 150 µg intrathecally provided analgesia which extended upto 6 hours in 50% of their patients who underwent caesarean section [16]. The longer duration of pain free interval in our patients was probably because hysterectomy was done vaginally thereby avoiding the abdominal incision which is painful. In the study by Shah, et al. the analgesic duration was extended upto 21.33 ± 12.69 hours with the intrathecal injection of midazolam 2 mg, buprenorphine 150 µg and bupivacaine in patients who underwent lower abdominal surgery [17]. In another study in patients who underwent caesarean section with intrathecal lignocaine 65-70 mg with 0.2 mL of buprenorphine as an adjuvant, the mean pain free period of 17.65 hours was observed [18].

The average time taken for complete motor block in our study was 9.12 min ± 3.908 which was comparable with the study by Celleno, et al. [6].

When compared with the basal readings, there was a statistically significant fall in the HR, MAP and RR. Eight patients had one episode of bradycardia with HR<60 which was treated with IV atropine. Of these, two patients were on beta blockers for hypertension. Bradycardia was noted between 60 to 90 minutes of spinal block. Decreased venous return resulting in reduced right atrial pressure (Bainbridge Reflex), blockade of cardiac accelerator fibres when the sympathetic block extends above T4 and preoperative beta blocker therapy have been implicated as some of the causes of bradycardia under spinal anesthesia [19, 20]. Occasional ectopics were observed in 4 patients. However, none of the patients had any adverse events.

One of the feared adverse effects of opioids is respiratory depression. Two patients had a respiratory rate of 8 and 10 per minute, 45 minutes after the subarachnoid block. The patient with RR of 8 had a basal RR of 16 and patient with RR 10 had a basal RR of 18.Both the patients were monitored in the recovery room for 24 hours with pulse oximetry and arterial blood gas analysis (ABG). The ABG readings were within normal limits with no hypercarbia or hypoxemia. The sedation score was between 3 to 2 in the first patient and 2 in other patient. The arterial oxygen saturation remained above 95 % in all the patients.

When compared to full agonists, such as morphine and fentanyl with respect to respiratory effect and analgesia, buprenorphine behaves very differently. Dahan, et al. observed that the concentration range that caused an increase in analgesia with morphine caused concentration-dependent respiratory depression without any plateau or ceiling [21]. However, in another study by the same author, it was observed that doubling the dose of buprenorphine increased its peak analgesic effect while the timing and magnitude of respiratory depression remained unchanged. Thus, buprenorphine displays a plateau for respiratory depression over a dose range where no plateau in analgesic effect is observed [22] this makes buprenorphine an attractive adjuvant.

Capogna, et al. have reported safe use of intrathecal buprenorphine 30 µg in elderly patients [23]. Buprenorphine being lipid soluble, when administered intrathecally passes rapidly via arachnoid granulations into venous and lymphatic vessels. Hence the rostral spread of the drug to the respiratory centre via the cerebrospinal fluid is minimized [24]. Balasubramanya, et al. have reported a case of

respiratory depression in a 38-year-old female who underwent abdominal hysterectomy under spinal block with bupivacaine 2.8 ml and buprenorphine 30µg [25].

Nausea and vomiting is one of the most distressing side effects of intrathecal buprenorphine which occurred in our patients also. However it was managed with IV ondensetron.

Urinary retention could not be assessed as all patients were catheterized at the end of the surgery and the catheter was removed after 24 hours.

Pruritus is one of the commonest side effects of neuraxial opioids. The incidence of mild pruritus was 20% when buprenorphine was administered intrathecally when compared to epidural administration where the incidence was 4% [16]. In our study the incidence of pruritus was 8.16% and was self-limiting.

The antishivering effect of opioids is mostly due to stimulation of Kappa receptors than µ receptors [26]. In a study where the antishivering effect of IV pethidine was compared with IV buprenorphine, pethidine was found to be more effective. However the authors concluded that buprenorphine decreased the severity of shivering [27]. In our study only 5 patients had mild shivering.

Conclusion

To the best of our knowledge, no studies have reported the use of 150 µg of buprenorphine intrathecally for vaginal hysterectomy. A single dose of intrathecal buprenorphine 150 µ added to bupivacaine provides analgesia for a significant length of time in patients who have undergone vaginal hysterectomy.

References

1. Balakrishnan D, Dibyajyoti G. A comparison between non-descent vaginal hysterectomy and abdominal hysterectomy. Journal of Clinical and Diagnostic Research. J Clin Diagn Res., 2016; Jan10(1): QC 11-QC 14.
2. Shaikh SI, Kiran M. Intrathecal buprenorphine for post-operative analgesia: A prospective randomized double blind study. J Anaesth Clin Pharmacol., 2010; 26: 35-8.
3. Gupta R, Verma R, Bogra J, Kohi M, Raman R, Kushwaha JK. A comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to bupivacaine. J Anaesth Clin Pharmacol., 2011; 27: 339-43.
4. Budd K, Collett. Old dog-new(ma)trix (editorial). Br J Anaesth., 2003; 90: 722-24.
5. Cowan A, Friedrichs E, StraBburger W, Raffa RB. Basic pharmacology of buprenorphine. In Budd K, Raffa RB. eds Buprenorphine-The unique opioid analgesic. Stuttgart: Georg Thieme Verlag., 2005, p. 3-21.
6. Celleno D, Capogna G. Spinal buprenorphine for postoperative analgesia after caesarean section. Acta Anaesthesiol Scand., 1989; 33: 236-8.
7. Miwa Y, Yonemura E, Fukushima K. Epidurally administered buprenorphine in the perioperative period. Can J Anaesth., 1996; 43: 907-13.
8. Lalla RK. Low dose intrathecal buprenorphine for postoperative analgesia. Indian J Anaesth., 1997; 41: 38-9.
9. Breen TW, Shapiro T, Glass B, Foster-Payne D, Oriol NE. Epidural anesthesia for labor in an ambulatory patient. Anesth Analg., 1993; 77: 919-24.
10. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. BMJ, 1974; 2: 656-659.
11. Moore RA, Bullingham RES, McQuay HJ, Hand CW, Aspel JB, Allen MC, Thomas D, et al. Dural permeability to narcotics: in vitro determinationand

application to extradural administration. Br J Anaesth., 1982; 54: 1117-28.
12. Christoph T, Kogel B, Schiene K, Meen M, De Vry J, Friderichs E. Broad analgesic profile of buprenorphine in rodent models of acute and chronic pain. Eur J Pharmacol., 2005; 507: 87-98.
13. Yaksh, TL. Spinal opiate analgesia: characteristics and principles of action. Pain, 1981; 11: 293-346.
14. Tung AS, Yaksh TL. The antinociceptive effects of epidural opiates in the cat: studies on the pharmacology and the effects of lipophilicity in spinal analgesia. Pain, 1982; 12: 343-56.
15. Hambrook JM, Rance MJ. The interaction of buprenorphine with opiate receptor. In: Kosterlitz H ed. Opiate and endogenous opioid peptides. Amsterdam: Elsevier-North-Holland Biomedical, 1976; 295-301.
16. Ipe S, Korula S, Varma S, George GM, Abraham SP, Koshy LR. A comparative study of intrathecal and epidural buprenorphine using combined spinal-epidural technique for caesarean section. Indian J Anaesth., 2010; 54: 205-9.
17. Shah FR, Halbe AR, Panchal ID, Goodchild CS. Improvement in postoperative pain relief by the addition of midazolam to an intrathecal injection of buprenorphine and bupivacaine. Eur J Anaesthesiol., 2003; 20: 904-10.
18. Rabiee SM, Alijanpour E, Jabbari A, Rostami S. Benefits of using intrathecal buprenorphine. Caspian J Intern Med., 2014; 5: 143-7.
19. Carpenter RI, Caplan RA, Brown DI, Stephenson C, Wu R. Incidence and risk factors for the side effects of spinal anaesthesia. Anesthesiology, 1992; 76: 906-16.
20. Bromage P. Physiology and pharmacology of epiduralanalgesia. Anesthesiology, 1967; 28: 592-622.
21. Dahan A, Romberg R, Teppema L, Sarton E, Bijl H, Olofsen E. Simultaneous measurement and integrated analysis of analgesia and respiration after an intravenous morphine infusion. Anesthesiology, 2004; 101: 1201–9
22. Dahan A, Yassen A, Romberg R, Sarton L, Teppema L, Olofsen E, Danhol M. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth., 2006; 96: 627-32.
23. Capogna G, Celleno D, Tagariello V, Loffreda-Mancinelli C. Intrathecal buprenorphine for postoperative analgesia in the elderly patients. Anaesthesia, 1988; 48: 128-30.
24. Fooley KM, Inturrisi CE. Opioid analgesics in the management of clinical pain. New York: Raven Press, 1986.
25. Balasubramanya H, Parimala. Intrathecal buprenorphine induced severe respiratory depression. Journal of Dental and Medical Sciences, 2014; 13(11): 43-44.
26. Baumann PL, Sung YF. Treatment of postoperative shivering in an ambulatory surgery center (ASC). Anesthesiology, 1992; 77: A46.
27. Parsa T, Dabir S, Radpay B. Efficacy of pethidine and buprenorphine for prevention and treatment of post anesthetic shivering. Tanaffos, 2007; 63(3): 54-8.