Efficacy of dexmedetomidine in reducing postoperative morphine consumption in patients undergoing total abdominal hysterectomy

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ABSTRACT

Introduction: Dexmedetomidine is an alpha-2-adrenergic receptor agonist and neither has respiratory depressant effect nor addictive potential. These favourable properties are useful following major surgical procedures that are associated with significant morbidity caused by pain. This prospective, randomised, double-blinded placebo controlled study was conducted in patients undergoing total abdominal hysterectomy to determine the efficacy of two different doses of intraoperative dexmedetomidine infusions in reducing the amount of morphine consumption during the first 24 hour postoperative period. **Materials and Methods:** Sixty ASA I or II patients aged between 35 to 60 years were randomised into three groups to receive intraoperative infusions of dexmedetomidine 0.3 µg/kg/hr (Group A), dexmedetomidine 0.5 µg/kg/hr (Group B) or normal saline as placebo (Group C) without any loading dose, immediately after induction of anaesthesia. Haemodynamic parameters (heart rate and mean arterial pressure) were recorded prior to induction of anaesthesia and at 15 minute intervals intraoperatively. Patients were given patient-controlled analgesia with morphine after surgery and morphine consumption was recorded at 6, 12 and 24 hours postoperatively. **Results:** Group A and B showed a significant reduction in morphine consumption, compared to Group C and a higher percentage of reduction was noted in Group B as compared to Group A. Group B showed a significant 33% reduction at the 24 hour postoperative period. Mean heart rates were significantly lower in both Group A and B however none of the patients required any rescue drugs. There were no significant differences observed in MAP in all three groups. No side effects were reported. **Conclusion:** Intraoperative dexmedetomidine infusion of 0.5 µg/kg/hr significantly reduces postoperative morphine consumption when compared to 0.3 µg/kg/hr without causing significant haemodynamic instability and side effects.

Keywords: Dexmedetomidine, morphine, total abdominal hysterectomy, drug adverse effect

INTRODUCTION

Dexmedetomidine is an alpha-2-adrenergic receptor agonist with similar effects to that of clonidine. As a full agonist, dexmedetomidine is more potent when compared to its partial agonist counterpart, clonidine in which the affinity of dexmedetomidine for the alpha-2-adrenoreceptor is higher (ratio of α_2/α_1:1600/1) with a shorter duration of action. [1] Dexmedetomidine has been widely used in the United States since 1999 for short term seda-

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tion in mechanically ventilated patients. [1] Apart from sedative properties, its clinical effects also include analgesia and sympatholytic properties. The primary analgesic effects and potentiation of opioid-induced analgesia result from activation of postsynaptic alpha-2 -adrenergic receptors in the dorsal horn of the spinal cord. It increases potassium ion conductance across its channels and inhibits substance P release to decrease nociceptive transmission. [1] Dexmedetomidine is an attractive adjunct to opioid analgesics as it neither has respiratory depressant effect nor addictive potential. These favourable properties make dexmedetomidine useful in patients following major surgical procedures that are associated with significant morbidity caused by pain. [2]

Total abdominal hysterectomy (TAH) alone or with bilateral salphingo-oophorectomy (TAHBSO) is associated with significant postoperative pain. Effective postoperative pain management can reduce discomfort with improved patients' satisfaction leading to earlier mobilisation, shortened hospital stay and reduction in hospital costs. [3] Since 2011, the importance of pain relief was widely recognised, whereby pain scoring became mandatory and was implemented as the fifth vital sign to be charted in all Malaysian government hospitals. [4] Pain score is considered as an important component in patients' postoperative discharge criterion from the recovery area. [5] Patients with a pain score of less than four are allowed to be discharged from the operation theatre to the wards in our local hospital setting.

TAHBSO is generally performed under general anaesthesia (GA). Patients are given either an epidural infusion or a patient controlled analgesia device with morphine (PCAM) as postoperative pain relief. Unfortunately, PCAM use may be associated with sedation, nausea, vomiting, respiratory depression, urinary retention or pruritus. These morphine induced adverse effects potentially result in increased morbidity postoperatively including delayed mobilization and prolonged hospitalisation. Previous studies have demonstrated that intraoperative infusion of intravenous (IV) dexmedetomidine significantly reduces postoperative morphine consumption. This multi-modal analgesic benefit not only reduces opioid induced side effects but that of dexmedetomidine adverse effects as well. [1, 2, 6, 7] However, there are studies showing significant findings of haemodynamic changes when a loading dose of dexmedetomidine was given prior to the infusion. [8, 9]

The aim of this study was to determine the efficacy between efficacy of two doses of intraoperative dexmedetomidine infusion; 0.3 µg/kg/hr versus 0.5 µg/kg/hr in reducing the initial 24 hour postoperative morphine consumption. In the same setting, intraoperative haemodynamic changes and occurrence of postoperative side effects were additionally taken into account.

MATERIALS AND METHODS

This was a prospective, randomised, double-blind study conducted following approval from the Research and Ethics Committee in Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and Ministry of Health, Malaysia. A total of 60 female patients aged between 30 to 65 years planned for TAH or TAHBSO under GA were recruited. All patients had a physical status of American Society of Anesthesiologists (ASA) I or II with normal hepatorenal biochemistry profiles. Patients with a history of chronic drug or alcohol abuse, mental illness or treatment with psychotropic medications, allergies to the study drug, baseline heart rate (HR) less than 50 beats per minute or those on beta blocker agents and obese patients whose body mass index (BMI) exceeded 35 kg/m^2 were excluded.

During the preoperative rounds, patients were assessed and explained on the

study protocol, visual analogue scale (VAS) and the proper use of the PCAM device. Written informed consent was obtained from all patients. All recruited patients were fasted from 12 midnight and received oral midazolam 3.75 mg on the night prior to surgery. They were subsequently randomised into three groups. Patients in Group A and B were given dexmedetomidine infusion at 0.3 µg/kg/hr and 0.5 µg/kg/hr respectively. Group C patients were given a normal saline infusion at a similar rate to Group A, acting as a placebo. All study drugs were prepared by the primary investigator after randomisation.

In the operating room, standard ASA monitoring equipment were established for all patients. Baseline haemodynamic parameters such as HR and mean arterial pressure (MAP) were recorded prior to induction of anaesthesia and at every 15 minute intervals throughout anaesthetic maintenance until the end of surgery. All patients were induced with GA using IV fentanyl 2 µg/kg, IV propofol 2 mg/kg followed by IV rocuronium 0.6 mg/kg to facilitate endotracheal intubation after 3 minutes of pre-oxygenation. Anaesthesia was maintained with sevoflurane in a mixture of oxygen and air at a minimum alveolar concentration of 0.8–1.0. All patients received their study drug infusion from a pre-prepared syringe via a Terumo® infusion pump according to their allocated groups immediately after induction. All patients received IV morphine 0.1 mg/kg, 10 minutes after induction of anaesthesia and IV parecoxib 40 mg, 30 minutes before the end of surgery. Intermittent boluses of IV fentanyl 25 µg were administered accordingly as rescue analgesia when intraoperative pain relief was deemed inadequate by the attending anaesthetist. All patients also received IV dexamethasone 0.1 mg/kg during induction and IV granisetron 1 mg, 30 minutes before the end of surgery as postoperative nausea and vomiting prophylaxis.

Hypotension, which was taken as a decrease in baseline MAP of more than 20% was treated initially with 10 ml/kg of IV crystalloid. Those who were unresponsive to the fluid boluses were given aliquots of either IV ephedrine 6 mg or IV phenylephrine 100 µg when needed. Intravenous atropine 0.4 mg bolus was given in the event of significant bradycardia, which was defined as a reduction of 20% from the baseline HR with concurrent hypotension. All intraoperative rescue drugs were given repeatedly as required and these requirements were documented. Infusion of the study drug was stopped once closure of the abdominal muscle began. At the end of surgery, neuromuscular block was antagonized with IV neostigmine 2.5 mg and IV atropine 1 mg to assist in extubation of the trachea.

All patients' vital signs were monitored in the standard manner at the recovery area for 30 minutes. Patients' pain scores were assessed by multiple anaesthetic trainee officers in charge who were blinded to the study drug. The pain scores upon arrival in the recovery area and before being discharged to the ward were recorded with a standard VAS ranging from 0 to 10 in which 0 = no pain and 10 = worst pain imaginable. Level of consciousness was assessed with sedation score chart ranging from 0 – 4 in which 0 = awake and alert, 1 = mild, wakes instantly to call, 2 = drowsy, arouses with shaking, 3 = very drowsy, difficult to arouse and 4 = sleeping. The PCAM device set at bolus dose of 1mg/ml and a lock-out period of 5 minutes, without any background infusion was commenced in a dedicated IV access when the sedation score was less than two. The amount of morphine required was recorded and patients were discharged from the recovery area if the pain score was less than 4.

All patients were followed up by the Acute Pain Service team in the ward where their vital signs, pain scores, amount of mor-

phine consumption via the PCAM device were monitored and charted at 6, 12 and 24 hours postoperatively. Any incidence of adverse effects such as sedation, respiratory depression, bradycardia, hypotension, urinary retention and pruritus were recorded and treated accordingly. As part of multimodal pain management, oral paracetamol 1 gm 6 hourly was administered routinely to all patients.

Previous studies have showed that dexmedetomidine was able to reduce morphine consumption in the postoperative period by 40-60%. [1, 2, 6] We considered a 30% reduction of morphine consumption to be statistically significant. The sample size was calculated using the standard deviation of 10.7 from a previous study. [2] A power of the study of 80% was taken to detect a significant level set at 5%, including a 15% dropout rate in which a total of 60 patients were required.

Data collected were analysed using the Statistical Package for the Social Sciences 22.0 ™ Software (SPSS, IBM). Demographic data and postoperative morphine consumption were analysed using analysis of variance (ANOVA). The changes in MAP and HR were analysed using ANOVA for repeated measurements. The rescue drugs required and the incidence of side effects were analysed using the chi-square test. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

A total of 60 patients were enrolled in this study. There were no statistically significant differences with regards to age, BMI, race and ASA status among the three groups as shown in Table 1.

TABLE 1: Demographic data of participants)

	Group A (n=20)	Group B (n=20)	Group C (n=20)
Age (years)	47.6 ± 7.0	45.0 ± 4.7	48.1 ± 8.2
BMI (kg/m^2)	25.1 ± 2.2	23.8 ± 2.6	23.8 ± 2.5
Race			
Malay	7 (35.0)	7 (35.0)	7 (35.0)
Chinese	8 (40.0)	6 (30.0)	6 (30.0)
Indian	5 (25.0)	6 (30.0)	7 (35.0)
Others	0 (0.0)	1 (5.0)	0 (0.0)
ASA			
I	9 (45.0)	10 (50.0)	10 (50.0)
II	11 (55.0)	10 (50.0)	10 (50.0)

Values are expressed as mean ± standard deviation (SD), number (n) and percentage in parenthesis.
ASA: American Society of Anaesthesiologist

In Table 2, the reduction of morphine consumption at 6 hours in Group B was significantly lower when compared to Group A and C (p<0.001). However there was no statistically significant reduction of morphine consumption between Group A and Group C at the 6 hour postoperative period. Conversely, there was a significant reduction of morphine consumption among the three groups at the 12 hour and 24 hour postoperative period (p<0.001, p=0.002).

The mean HR among the three groups was similar at baseline as shown in Figure 1a. The intraoperative mean HR in Group A and Group B were significantly lower when compared to the baseline (p<0.001). No significant differences in mean HR between Group C and baseline. Although the mean HR between

TABLE 2: Postoperative morphine consumption (mg).

Time (hours)	Group A (n=20)	Group B (n=20)	Group C (n=20)	*p* value
6	11.2 ± 1.9	7.6 ± 2.0 * □	11.7 ± 1.6	<0.001 * □
12	16.2 ± 2.0 #	12.3 ± 2.2 * □	19.5 ± 4.0	<0.001 * □, 0.002 #
24	21.4 ± 2.6 #	17.1 ± 1.76 * □	25.7 ± 4.1	<0.001 * □ #

Values are expressed as mean ± SD
Significant difference between Group B and Group C; # Significant difference between Group A and Group C;
□ Significant difference between Group A and Group B

Group A and Group B throughout the surgery at each 15 minute interval were not significant, both had a significantly lower HR trend when compared to Group C.

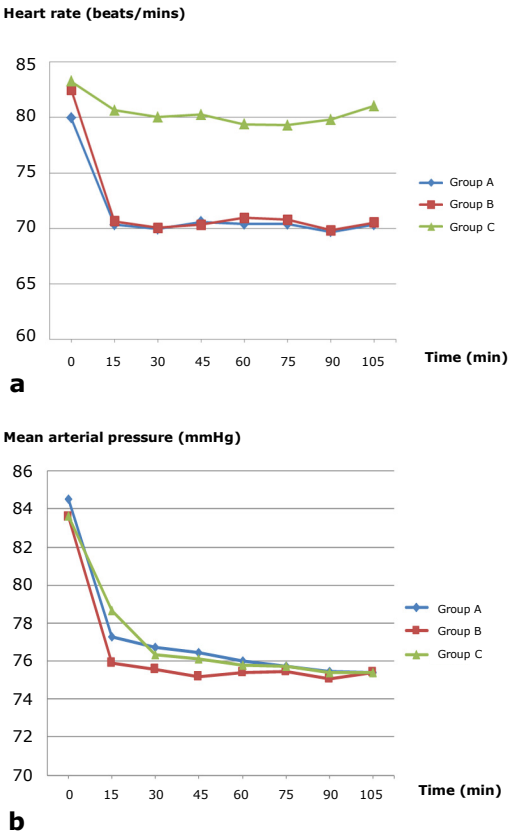
The MAP at baseline among the three groups was similar as shown in Figure 1b. All groups intraoperative MAP were significantly lower than baseline (p<0.001). However there were no significant differences seen when compared among the three groups.

No vasopressors or atropine were required as rescue treatment in all three groups. Only one patient each in Group A and Group C required intraoperative IV fentanyl as rescue analgesia. There were no postoperative adverse effects documented in all patients among the three groups.

DISCUSSION

In our study, both doses of dexmedetomidine infusions significantly reduced the morphine consumption at the 12 and 24 hours postoperative period when compared to placebo. A reduction in morphine usage by 17% and 33% was obtained in Group A and Group B respectively at 24 hours. Similarly, Gurbet *et al.* reported a 57% reduction in postoperative morphine consumption at 48 hours. [2] We further showed that dexmedetomidine infusion at 0.5 µg/kg/hr have a superior effect when compared to dexmedetomidine 0.3 µg/kg/hr as demonstrated by the higher percentages of morphine consumption reduction at all the 6, 12 and 24 hours postoperative period. Although the study by Al-Dehayat *et al*. did not show significant morphine consumption reduction at the 24 hour period, their patients in the morphine alone group had received significantly more morphine in the recovery area to achieve equi-analgesic dose as received by the dexmedetomidine group. [7]

An animal study done by Ansah *et al*. reported that increasing serum concentrations of dexmedetomidine increased its analgesic



Figs. 1: a) Trends in intraoperative mean heart rate (HR), and b) Mean arterial pressure (MAP) among the 3 groups.

effects. [10] To date, no similar study to assess analgesic effects has been done on human subjects. In our study, we did not measure the serum concentration of dexmedetomidine between Group A and Group B. One patient each in Group A and C required additional IV fentanyl as rescue analgesia intraoperatively which may suggest that a higher concentration of dexmedetomidine confers a greater analgesic effect however this finding was not statistically significant.

Infusion doses of dexmedetomidine were used in this study without an initial loading dose to avoid potential haemodynamic instability. Previous studies found more derangement in the HR and MAP after a loading dose of 1 µg/kg dexmedetomidine. [8, 9] Ickeringill *et al.* administered a dexmedetomidine infusion ranging between 0.2–0.4 µg/kg/hr

and found that omitting the loading dose avoided undesirable haemodynamic effects without compromising sedation and analgesia. [11]

A review reported that most of the adverse effects of dexmedetomidine may be prevented by omitting or slowing the administration rate of the loading dose. [12] Kunisawa *et al.* demonstrated that the systolic blood pressure was decreased after administration of a loading dose of dexmedetomidine 1 μg/kg over 10 minutes in hypovolaemic patients especially in those who were anxious or in pain upon arrival to the operating room. [9] Gurbet *et al*. did not report any significant changes in MAP or HR from baseline after a much slower loading dose of dexmedetomidine over 30 minutes. [2] On the contrary, Arain *et al.* found a transient increase in MAP during the initial dexmedetomidine loading dose of 1 μg/kg followed by a progressive decrease throughout the 10 minutes loading duration.[8] However, there were no significant differences in intraoperative MAP despite lower HR trends observed in the dexmedetomidine group when infused at 0.4 μg/kg/hr. The increase in blood pressure has been postulated to be due to the stimulation of the alpha-2 -b receptors in vascular smooth muscle that causes vasoconstriction. This transient increase is normally associated with a reflex bradycardia. [12]

Comparable results were obtained in our study where we found an average decrease in mean HR of 11% in both dexmedetomidine groups when compared to the control group. There were no significant differences in mean HR reduction between both dexmedetomidine infusion groups. Bradycardic effect of dexmedetomidine has been reported to be due to reduced sympathetic tone and simultaneous enhanced vagal activity. [12] Actions on presynaptic alpha-2 receptors by dexmedetomidine can result in overall reduction of noradrenaline release leading to a fall in blood pressure and heart rate. In our study, this decrease in HR however was not associated with any significant reduction in MAP. The drop in HR did not require any rescue drugs. In fact, an overall reduction of MAP from baseline was observed in all the three groups and was comparable throughout the surgery which suggested that these reductions may not be due to the dexmedetomidine infusion per se. Other factors that may have contributed to the reduction in MAP was postulated to be due the effect of volatile anaesthetic agent, intraoperative fluid and blood loss.

None of the patients in our study experienced any adverse effects such as sedation, pruritus, respiratory depression, hypotension, bradycardia or urinary retention in the postoperative period at both infusion doses. Thus it could be recommended that dexmedetomedine at the dose of 0.5 μg/kg/hr be used as an adjunct in reducing postoperative morphine consumption without causing any side effects.

There were limitations in this study. Patients scheduled for either TAH or TAHBSO surgeries performed by different surgeons, with differences in type of skin incision and extent of surgical procedure in the lower abdomen may contribute to dissimilar pain perception. Differing thresholds and perception of pain among patients may also result in variation in postoperative morphine consumption. Multiple operators were involved in conducting this study in the intraoperative and postoperative stages which might have led to bias in the study.

In conclusion, both dexmedetomidine infusions significantly reduced the amount of postoperative morphine delivered by the PCAM device after TAH/TAHBSO. However the 0.5 μg/kg/hr infusion was found to be more effective than the 0.3 μg/kg/hr infusion. Both infusion groups were associated with reduc-

tions in HR without significant changes in MAP. No side effects were reported with both infusions.

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