

## Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia

T.-F. Lin, Y.-C. Yeh, F.-S. Lin, Y.-P. Wang, C.-J. Lin, W.-Z. Sun\* and S.-Z. Fan

Department of Anaesthesiology, National Taiwan University Hospital, No. 7, Chung San South Road, Taipei, Taiwan, Republic of China

\*Corresponding author. E-mail: wzsun@ntu.edu.tw

**Background.** Perioperative use of dexmedetomidine is associated with reduction in postoperative analgesic requirements. This study examined whether dexmedetomidine added to i.v. patient-controlled analgesia (PCA) morphine could improve analgesia while reducing opioid-related side-effects.

**Methods.** In this double-blinded, randomized, controlled study, 100 women undergoing abdominal total hysterectomy were allocated to receive either morphine 1 mg ml<sup>-1</sup> alone (Group M) or morphine 1 mg ml<sup>-1</sup> plus dexmedetomidine 5 µg ml<sup>-1</sup> (Group D) for postoperative i.v. PCA, which was programmed to deliver 1 ml per demand with a 5 min lockout interval and no background infusion. Cumulative PCA requirements, pain intensities, cardiovascular and respiratory variables, and PCA-related adverse events were recorded for 24 h after operation.

**Results.** Compared with Group M, patients in Group D required 29% less morphine during the 0–24 h postoperative period and reported significantly lower pain levels from the second postoperative hour onwards and throughout the study. Whereas levels of sedation were similar between the groups at each observational time point, decreases in heart rate and mean blood pressure from presurgery baseline at 1, 2, and 4 h after operation were significantly greater in Group D (by a range of 5–7 beats min<sup>-1</sup> and 10–13%, respectively). The 4–24 h incidence of nausea was significantly lower in Group D (34% vs 56.3%,  $P < 0.05$ ). There was no bradycardia, hypotension, oversedation, or respiratory depression.

**Conclusions.** The addition of dexmedetomidine to i.v. PCA morphine resulted in superior analgesia, significant morphine sparing, less morphine-induced nausea, and was devoid of additional sedation and untoward haemodynamic changes.

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Maximizing pain relief and minimizing analgesic-related side-effects are vital to patient recovery after surgery. A multimodal approach, using different classes of analgesics, is the currently recommended method to obtain this goal.<sup>1</sup> Of the multimodal protocols, combining an adjunct drug with an opioid in i.v. patient-controlled analgesia (PCA) as a convenient regimen for pain management is gaining worldwide popularity in current clinical practice. Various adjunct drugs, including antiemetic,<sup>2</sup> non-steroidal anti-inflammatory drugs,<sup>3</sup> pure opioid-antagonist,<sup>4</sup> opioid agonist–antagonist,<sup>5</sup> and ketamine,<sup>6</sup> have been used in such

a multimodal effort. However, dexmedetomidine, a potent and highly selective  $\alpha_2$ -adrenoreceptor agonist possessing multifaceted attributes of analgesia, anxiolysis, sedation, sympatholysis, and no respiratory depression,<sup>7–10</sup> coadministered with morphine by way of PCA has not yet been investigated.

The aim of this study was to evaluate whether dexmedetomidine added to PCA morphine could enhance analgesia while reducing side-effects related to PCA morphine administration. Side-effects related to the dexmedetomidine–morphine mixture were also investigated.

## Methods

After institutional review board approval of this randomized double-blinded controlled study, informed consent was obtained from 100 female patients aged between 18 and 65 yr, ASA I or II, undergoing total abdominal hysterectomy with general anaesthesia. Patients were excluded if there was a history of hypertension, ischaemic heart disease, or conduction disturbance, if they were taking antidepressants or  $\beta$ -adrenoreceptor blockers, if they had underlying gastrointestinal diseases, a history of previous postoperative nausea and vomiting, motion sickness, or a known sensitivity to any of the medications used.

Our hospital pharmacy was in charge of the study medication preparation and group assignment. A computer-generated randomization table was used to allocate patients into two groups ( $n=50$  per group). The 100 ml solution in the PCA reservoir bag contained 100 mg of morphine in normal saline ( $1 \text{ mg ml}^{-1}$ ) in Group M or 100 mg morphine plus 500  $\mu\text{g}$  of dexmedetomidine in normal saline (morphine  $1 \text{ mg ml}^{-1}$ ; dexmedetomidine  $5 \mu\text{g ml}^{-1}$ ) in Group D. The PCA dose of dexmedetomidine (Precedex<sup>®</sup>; Hospira, Inc., Lake Forest, IL, USA) was based on the  $0.5 \mu\text{g kg}^{-1} \text{ h}^{-1}$  infusion divided by six. This average number of PCA doses in the first hour after surgery was based on a prior study in a similar population.<sup>2</sup> Both patients and observers were blinded with respect to the group allocation. Double-blinding was achieved by labelling the PCA reservoir bags with a particular identification number only. The blinding code retained by the pharmacy was opened after completion of study. For reasons of patient safety, a sealed opaque envelope containing the treatment assignment was kept with the patient in the post-anaesthesia care unit (PACU) and general ward. Unblinding would be carried out when an unexpected serious adverse event (circulatory failure, conscious disturbance, and respiratory depression) occurred and this knowledge was required for emergency treatment.

Routine presurgery baseline heart rate (HR) and mean blood pressure (MBP) were documented after ward admission. Before the surgery, all patients were instructed on the operational use of PCA system (Lifecare 5500 PCA; Abbott Laboratories) and a 0–10 verbal rating scale (VRS), where 0 represented no pain and 10 the worst pain imaginable. The goal of PCA analgesia was to maintain the VRS at rest  $\leq 4$  between 4 and 24 h after operation. A standard general anaesthetic was given, comprising thiopental  $3\text{--}5 \text{ mg kg}^{-1}$ , fentanyl  $1.5\text{--}3 \mu\text{g kg}^{-1}$ , and cisatracurium  $0.5\text{--}0.8 \text{ mg kg}^{-1}$ . Anaesthesia was maintained with isoflurane  $0.8\text{--}1.5\%$  in nitrous oxide  $60\%$  and oxygen  $40\%$ . Edrophonium  $0.5\text{--}1 \text{ mg kg}^{-1}$  and atropine  $0.015 \text{ mg kg}^{-1}$  were given to reverse residual neuromuscular block at the end of surgery. The patients were attached to a PCA machine upon arrival in the PACU. As soon as the patients were awake, their pain was assessed using the VRS. If the patient reported a VRS at rest of 5 or higher,

an anaesthetist not involved in the study titrated PCA solution i.v. 2 ml at 5 min intervals until the VRS was 4 or less. Then, the patients were encouraged to self-administer their own PCA medications. The setting for PCA was 1 ml bolus with a 5 min lockout. There was no background continuous infusion throughout the postoperative period. Patients were monitored and received nasal  $\text{O}_2$  supplementation. The HR,  $\text{SpO}_2$ , and MBP were recorded at specific time points (0, 15, 30, 45, and 60 min after arrival to the PACU) during the 1 h PACU stay.

Patients were assessed at 1, 2, 4, and 24 h after operation. The cumulative PCA requirements were recorded in PCA machines, and the data were transferred to a computer for interpretation. Pain intensity was evaluated with VRS at rest (VRSR) and upon movement (VRSM). Patients were asked to score their worst VRSR and VRSM since the previous assessment. VRSR was assessed with the patient lying supine and VRSM assessed during change from supine to lateral position. Nausea, vomiting, and pruritus were investigated by incidence and severity. The severity of an adverse event was defined as mild (discomfort noticed, but no disruption of anticipated normal activity), moderate (discomfort sufficient to reduce or affect anticipated normal activity), or severe (inability to perform anticipated normal daily activity).<sup>11</sup> Patients were made aware that rescue antiemetic (prochlorperazine 10 mg i.v.) and rescue antipruritic (diphenhydramine 30 mg i.v.) would be available on request. Level of sedation was assessed with a five-point scoring scale (0, fully awake; 1, drowsy, closed eyes; 2, asleep, easily aroused with light tactile stimulation or a simple verbal command; 3, asleep, arousable only by strong physical stimulation; and 4, unarousable).<sup>12</sup> Each patient was asked to grade satisfaction (yes/no) with pain relief at the end of PCA use.

PCA treatment was considered a failure if the VRSR remained  $>4$  during 4–24 h after operation or if patients required more than three administrations of rescue medications for nausea, vomiting, or pruritus.<sup>4</sup> Adjunctive analgesic with i.v. meperidine 50 mg or ketorolac 30 mg would be administered for insufficient analgesia. Persistent nausea, vomiting, or pruritus would warrant PCA termination with the patient then being switched to an alternate analgesic modality. PCA-related bradycardia (HR  $<50 \text{ beats min}^{-1}$ ), hypotension ( $>20\%$  decrease in MBP from presurgery baseline), somnolence (sedation score  $\geq 3$ ), and respiratory depression (ventilatory frequency  $<8 \text{ bpm}$  lasting for more than 10 min) were considered as severe adverse events. If severe adverse events occurred, the use of PCA was stopped immediately and the adverse effects were treated with appropriate treatment. Hypotension or bradycardia was treated with volume expansion, ephedrine, or atropine. Respiratory depression was treated with naloxone and oxygen.

The power calculation for the study was based on morphine consumption in the first 24 h after surgery, assuming

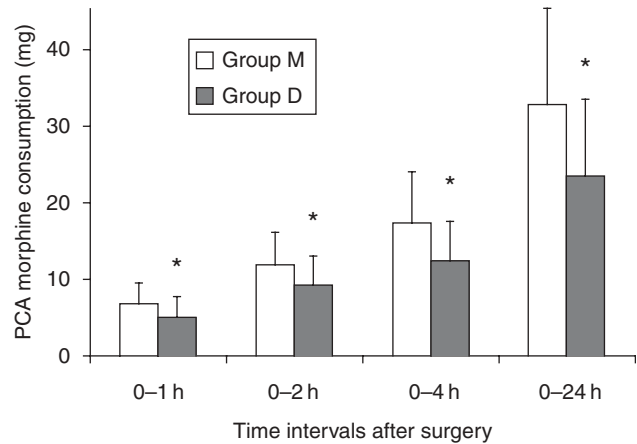
an opioid requirement of 27.5 (SD 11.5) mg in 24 h. This requirement was based on a prior study in a similar population.<sup>2</sup> To detect a 25% reduction in morphine requirements in the first 24 h after surgery, 45 subjects per treatment arm would be needed for a study with an alpha level of 0.5 (two-tailed) and a beta level of 0.2 (80% power). Patient characteristics, intraoperative data, cumulative morphine consumptions, HR, and MBP were analysed using Student's *t*-test. The incidence of adverse events, use of antiemetics or antipruritus, and patient satisfaction were analysed using the  $\chi^2$  test. Pain and sedation scores were analysed using the Mann–Whitney *U*-test. Changes in postoperative HR and MBP from presurgery baseline were analysed using the paired *t*-test. A probability level of <0.05 was considered to be statistically significant.

### Results

A total of 100 patients were recruited in this study. Two patients in Group M discontinued the investigation: one required reoperation within 24 h of surgery to stop postoperative haemorrhage and the other had severe dizziness that was judged more likely to be caused by anaemia. Ninety-eight patients completed the study: 48 in Group M and 50 in Group D. There were no significant differences with regard to patient characteristics and intraoperative variables between the two groups (Table 1).

Patients in Group D required significantly less PCA morphine than those from Group M at all times in the study (Fig. 1). During the 0–24 h postoperative period, cumulative PCA morphine use was 29% less in Group D than in Group M [23.3 (SD 10) vs 32.8 (12.4) mg, *P*<0.01]. The overall (0–24 h) dose of dexmedetomidine consumed in Group D was 116.5 (50)  $\mu$ g. Pain intensities, either VRSR or VRSM, were consistently significantly lower in Group D than in Group M from the second postoperative hour onwards and throughout the study (Table 2). Two patients in Group M reported insufficient analgesia and received adjunctive analgesics.

Compared with Group M, Group D patients had slower HR at 2 and 4 h after operation (Fig. 2A). Furthermore, a



**Fig 1** Cumulative doses of PCA morphine consumption. Data are mean (SD). \**P*<0.01, Group D vs Group M.

more significant decrease in HR below presurgery baseline occurred in Group D (range 5–7 beats  $\text{min}^{-1}$ ) at 1, 2, and 4 h after operation (Fig. 2B). Similarly, compared with Group M, Group D patients had lower MBP 45 min after surgery and at 1, 2, 4, and 24 h after operation (Fig. 3A). A more significant decrease in MBP below presurgery baseline occurred in Group D (range 10–13%) at 1, 2, and 4 h after operation (Fig. 3B). No patient experienced hypotension or bradycardia.

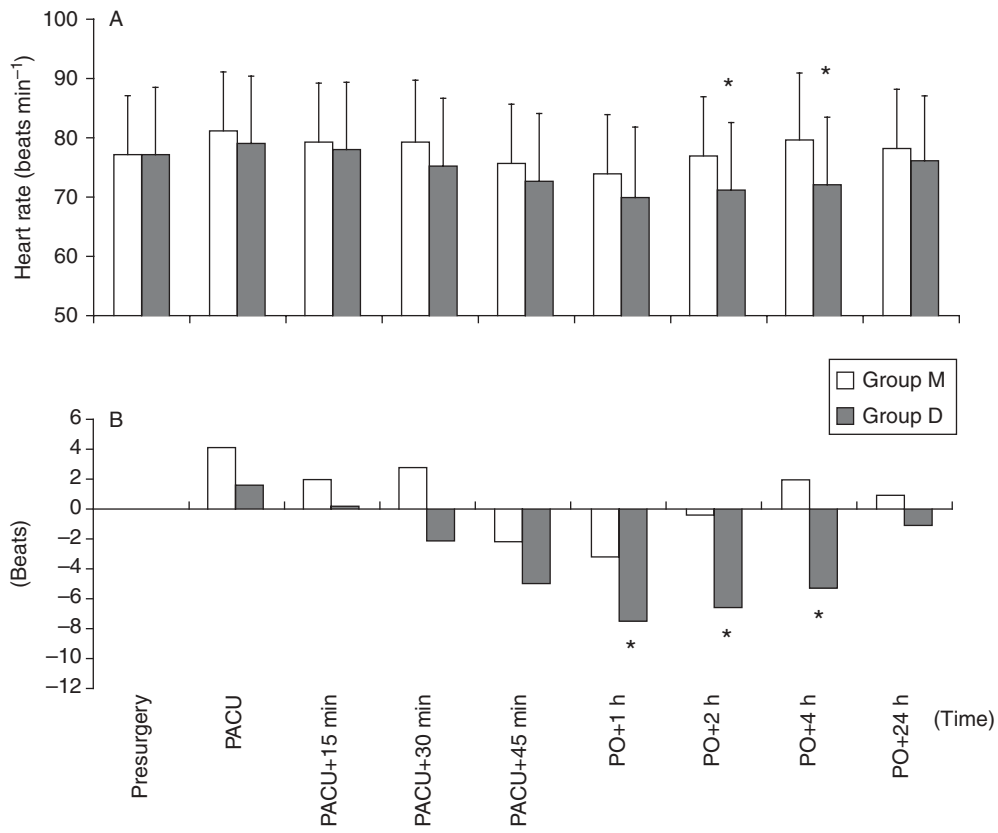
Main adverse events are reported in Table 3. Compared with Group M, the overall (0–24 h) incidence of nausea and vomiting was not significantly different in Group D. However, the incidence of nausea during the 4–24 h period was significantly lower in Group D than in Group M (34% vs 56.3%, *P*<0.05). Furthermore, the overall incidence of severe nausea was significantly lower in Group D than in Group M (6% vs 20.8%, *P*<0.05). The incidence of vomiting during the 4–24 h (18% vs 33%, *P*=0.106) and the overall incidence of severe vomiting (6% vs 17%, *P*=0.117) were also lower in Group D than in Group M, but the differences were not significant. The incidence and severity of pruritus and the sedation scores were all similar between the two groups. More patients in Group D were satisfied with the PCA therapy compared with Group M (94% vs 81.3%, *P*=0.068). There was no report of

**Table 1** Patient characteristics and intraoperative data. Values are median (range), mean (SD), or number. All variables were similar between the two groups

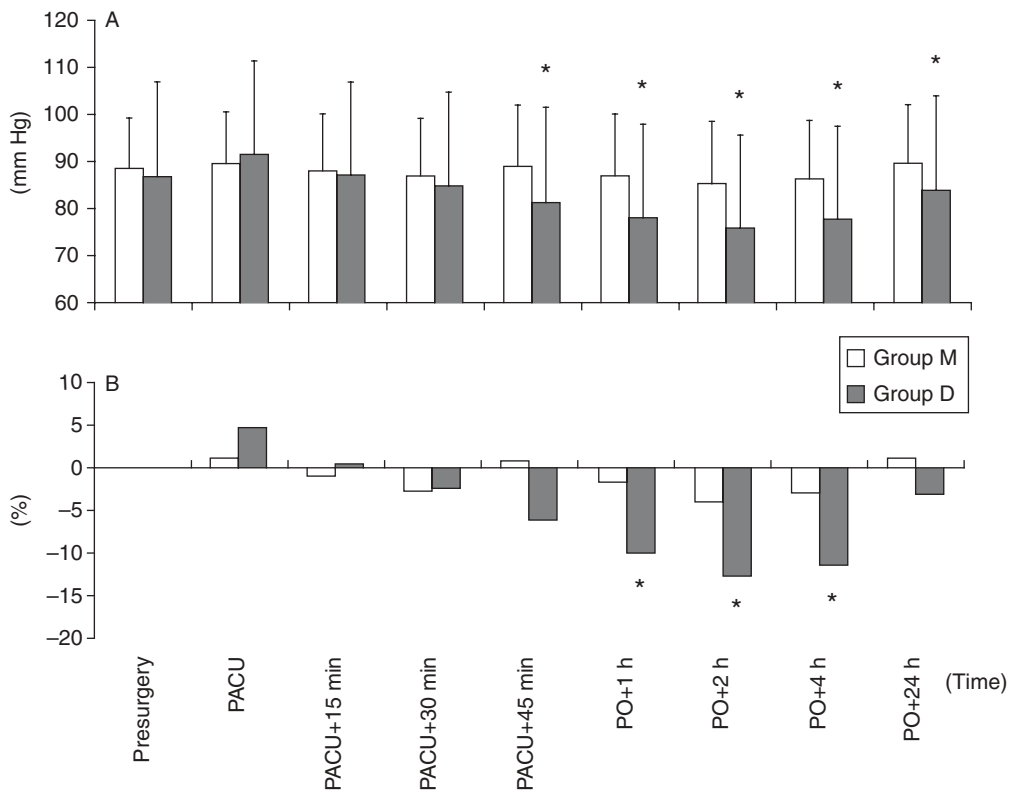
	Group M	Group D
Number	48	50
Age (yr)	43.5 (25–59)	43.5 (25–57)
ASA (I/II)	23/25	19/31
Height (cm)	157.4 (5.4)	158.1 (5.3)
Weight (kg)	58.9 (8.3)	57.8 (7.9)
Intraoperative data		
Duration of anaesthesia (min)	132 (31)	127 (35)
Fentanyl ( $\mu$ g)	150.5 (26.5)	144 (34.5)
Estimated blood loss (ml)	334 (422)	375 (298)
Fluids (ml)	1803 (902)	1901 (883)

**Table 2** VRSR and VRSM. Values are median (inter-quartile range). \**P*<0.05 and \*\**P*<0.01, Group D vs Group M

	Group M	Group D
At rest		
1 h	3 (2–4)	3 (1–4)
2 h	3 (1–3)	2 (0–3)*
4 h	3 (2–4)	2 (1–3)*
24 h	2 (1–2)	2 (1–2)**
Upon movement		
1 h	6 (5–7)	5 (5–6)
2 h	6 (4–7)	5 (4–5)**
4 h	5 (4–6)	4 (3–5)**
24 h	4 (4–5)	4 (3–4)**



**Fig 2** HR and HR changes. Data are mean (SD) or mean. \* $P < 0.05$ , significant inter-group differences (A) and significant intra-group differences compared with presurgery baseline (B).



**Fig 3** MBP and MBP changes. Data are mean (SD) or %. \* $P < 0.05$ , significant inter-group differences (A) and significant intra-group differences compared with presurgery baseline (B).

**Table 3** Main adverse events and rescue antiemetic/antipruritic requirements. Data are number of patients or %. Sedation scores: 0, fully awake; 1, drowsy, closed eyes; 2, asleep, easily aroused with light tactile stimulation or a simple verbal command; 3, asleep, arousable only by strong physical stimulation; and 4, unarousable. \* $P < 0.05$ , Group D vs Group M

	Group M	Group D
Number	48	50
Nausea		
0–24 h	33 (69)	30 (60)
0–4 h	22 (46)	20 (40)
4–24 h	27 (56)	17 (34)*
Severe nausea (0–24 h)	10 (21)	3 (6)*
Vomiting		
0–24 h	18 (38)	15 (32)
0–4 h	9 (19)	9 (18)
4–24 h	16 (33)	9 (18)
Severe vomiting (0–24 h)	8 (17)	3 (6)
Patients requiring prochlorperazine	12 (25)	9 (18)
Pruritus (0–24 h)	9 (19)	8 (16)
Patients requiring diphenhydramine	3	1
Sedation (0/1/2/3/4)		
1 h	28/12/8/0/0	22/13/15/0/0
2 h	34/8/6/0/0	31/11/8/0/0
4 h	38/5/5/0/0	35/9/6/0/0
24 h	44/4/0/0/0	44/6/0/0/0

somnolence or respiratory depression in this study. None of the adverse events warranted terminating PCA use.

## Discussion

This study shows that the dexmedetomidine–morphine mixture significantly enhances the analgesic effect of morphine, reduces PCA morphine requirements and the coexisting morphine-induced nausea, without clinically relevant bradycardia or hypotension, oversedation, or respiratory depression.

In line with studies demonstrating opioid-sparing effects by dexmedetomidine,<sup>13–15</sup> our finding that patients receiving dexmedetomidine required 29% less PCA morphine adds further support to the analgesic effect of dexmedetomidine in clinical pain. Agonism at  $\alpha_2$ -adrenoceptors in the spinal cord and in the locus ceruleus produces analgesia and sedation, respectively.<sup>7</sup> In the presence of these effects, it is difficult to distinguish whether analgesic or sedative effects are responsible for the reduced opioid requirements.<sup>16</sup> In our study, as sedation levels were similar between the groups, analgesic action rather than sedative effect was more likely to account for the morphine sparing by dexmedetomidine. Although all the patients were encouraged to push the PCA button to achieve an equal VRSR  $\leq 4$  between 4 and 24 h after operation, patients receiving dexmedetomidine–morphine mixture for PCA experienced significantly greater pain relief compared with those receiving only morphine for PCA. Improved analgesia by dexmedetomidine might come from the synergistic analgesic interactions with opioids,<sup>17</sup> reduction of stress,<sup>18</sup> and attenuation on the affective–motivational component (unpleasantness) of pain.<sup>10</sup>

The use of dexmedetomidine in the postoperative context after elective surgery might be complicated by potential concerns of unnecessary or even untoward sedation. Interestingly, we found no evidence of additional sedative effect by dexmedetomidine during the course of PCA use. There are possible explanations to this finding. First, doses of dexmedetomidine consumed in conjunction with morphine via PCA throughout the study were well within the lower half ranges of the recommended 0.2–0.7  $\mu\text{g kg}^{-1} \text{h}^{-1}$  maintenance infusion for intensive care sedation.<sup>19</sup> Simulating a 0.5  $\mu\text{g kg}^{-1} \text{h}^{-1}$  infusion in the first postoperative hour by means of PCA minidose titration, the mean doses of dexmedetomidine consumed ranged between 0.44  $\mu\text{g kg}^{-1} \text{h}^{-1}$  during 0–1 h, 0.36  $\mu\text{g kg}^{-1} \text{h}^{-1}$  during 1–2 h, 0.13  $\mu\text{g kg}^{-1} \text{h}^{-1}$  during 2–4 h, and 0.05  $\mu\text{g kg}^{-1} \text{h}^{-1}$  afterwards. Secondly, during the 0–4 h postoperative period when higher PCA doses were required to provide substantial analgesia, excessive sedation, if any, could have been counteracted by pain. Thirdly, the reduced cumulative PCA morphine requirements could also help mitigate sedation. Fourthly, the PCA-based drug delivery system, which has the distinct advantage of maintaining patients within their own therapeutic window by way of safe individual drug titration,<sup>20</sup> could also play a vital role in eliminating excessive sedation.

Haemodynamic changes after dexmedetomidine administration are complex. When given as a loading dose, it produces transient hypertension due to direct vasoconstriction, followed by more enduring hypotension and bradycardia.<sup>21</sup> When such a drug with direct cardiovascular effects is used as part of the postoperative analgesic regimen, concerns regarding the potentially deleterious haemodynamic effects might increase. Ickeringill and colleagues<sup>19</sup> reported that dexmedetomidine infusion without the loading dose avoided undesirable haemodynamic effects. For the purposes of this study, we chose to achieve postoperative pain relief via PCA alone. It is likely that omission of an intraoperative preloading dexmedetomidine dose might have helped reduce the susceptibility of patients to the negative chronotropic or pressure-lowering influences from residual general anaesthetics or subsequent PCA usage in the early postoperative period. In the present study, the use of dexmedetomidine–morphine mixture caused greater decreases in HR and MBP from presurgery baseline at 1, 2, and 4 h after operation. This may have been caused by the combined effects of the sympathoinhibitory effects of dexmedetomidine<sup>21</sup> and the direct peripheral dilation from morphine.<sup>22</sup> The magnitude of decrease in HR and MBP was not clinically relevant as it did not lead to bradycardia or hypotension warranting intervention.

The reduction in the incidence and severity of nausea is another benefit of combining dexmedetomidine and morphine in PCA. Sedation or drug-induced drowsiness has been implicated as a cause for relief from nausea by allowing the patient to ‘sleep it off’.<sup>23</sup> However, as the level of sedation was



similar between the two groups, decreased pain intensities along with reduced PCA morphine consumptions and thus fewer side-effects from opioids were more likely to account for the reduced nausea observed in Group D patients. However, the anti-nausea effect was apparent only when the assessment time point was relayed between 4 and 24 h after operation. The reasons for the lack of antiemetic benefits in the first 4 h could be a combination of the residual effect of anaesthetic on chemoreceptor trigger zone, the effect of pain on vomiting centre, or the effect of surgery.

In conclusion, the dexmedetomidine–morphine mixture reduced morphine consumption while yet improving the quality of analgesia. Decreased pain intensities together with the decrease in PCA morphine requirements results in reduced nausea induced by morphine and greater overall patient satisfaction with PCA. By PCA-based drug administration, use of the dexmedetomidine–morphine mixture is safe as it produces predictable postoperative haemodynamic alterations while eliminating unwanted oversedation. We suggest a novel protocol using dexmedetomidine as a valuable adjunct to morphine for postoperative PCA. Future dose-finding studies are warranted to strive for optimal balance between therapeutic effects and side-effects of this dexmedetomidine–morphine combination.

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