Journal of
Medical Sciences

Research Paper

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Antinociceptive Effect of ($α_2$-Adrenoceptor Agonist) Dexmedetomidine vs Meperidine, Topically, after Laparoscopic Gynecologic Surgery

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This prospective double blinded study compared the analgesic effect of intraperitoneal dexmedetomidine or meperidine with bupivacaine to intraperitoneal bupivacaine alone in laparoscopic gynecologic surgery. Sixty female patients undergone elective laparoscopic gynecologic surgery given a standardized general anesthesia were randomly allocated into one of three equal sized groups; Group B: intraperitoneal 50 mL bupivacaine 0.25%, Group B+M: intraperitoneal 50 mL bupivacaine 0.25%+1 mg kg^{-1} meperidine and Group B+D: intraperitoneal 50 mL bupivacaine 0.25%+1 µg kg^{-1} dexmedetomidine. The following parameters were evaluated: (1) Time to first request of analgesia, (2) The incidence and severity of postoperative shoulder pain for 24 h postoperatively, (3): The amount of postoperative PCA morphine for 24 h postoperatively. Times to first request of analgesia was significantly short in group B compared to the other 2 groups (p<0.05). Doses of intravenous PCA morphine consumed at 0-6, 6-12, 12-18, 18-24 and 0-24 h were significantly less in groups B+M and B+D compared to group B (p<0.05) with no significant difference between groups B+M and B+D. The incidence and severity of shoulder pain were less in group B+M and B+D compared to group B (p<0.05) with no significant difference between the later two groups. Intraperitoneal instillation of meperidine (1 mg kg^{-1}) or dexmedetomidine (1 µg kg^{-1}) in combination with bupivacaine 0.25% in female patients undergoing laparoscopic gynecologic surgery significantly decreases the postoperative analgesic requirements and decreased the incidence of shoulder pain compared to intraperitoneal bupivacaine 0.25% alone.

Key words: Intraperitoneal, bupivacaine, meperidine, dexmedetomidine, laparoscopic gynecologic surgery

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INTRODUCTION

Several indications and diseases in gynecology can be managed via laparoscopic surgery. Published reports have documented the advantages of laparoscopy over open surgery in nonblinded settings. The benefits of laparoscopic surgery claimed from these studies include a short hospital stay, a better cosmetic effect, less expensive and decreased postoperative pain (Lujan *et al.*, 2004; Nilsson *et al.*, 2000).

The incidence of postoperative shoulder pain following laparoscopic surgery may reach up to 80% and it represents a major cause for the high unanticipated admission rate (up to 12.1%) after day-case laparoscopic surgery (Hedayati and Fear, 1999). Diaphragmatic irritation by residual CO_2 gas probably explains the high incidence of postoperative shoulder pain (Kazama *et al.*, 1996). Some investigators have asserted that the intraperitoneal (IP) delivery of drugs is a simple and effective method of reducing the intensity of postlaparoscopic pain (Lee *et al.*, 2001). The intraperitoneal route of administration of local anesthetic is simple, does not involve additional central neuroaxial block and is particularly suited to the practice of ambulatory anaesthesia (Visalyaputra *et al.*, 2002).

α_2-Adrenergic agonists have been introduced to clinical anaesthesia for their sympatholytic, sedative, anaesthetic sparing and haemodynamic stabilizing properties (Tanskanen *et al.*, 2006). Combination of bupivacaine plus clonidine administered intraperitoneally in total abdominal hysterectomy operations provides more effective analgesia than bupivacaine alone during the early postoperative period (Memis *et al.*, 2005).

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist with both sedative and analgesic properties and is devoid of respiratory depressant effect. It has been used to premedicate and sedate patients undergoing day care procedures without adverse effects (Alhashemi, 2006). A recent study done on rats suggested that, Combination of topical COX-2 inhibitors with intraperitoneal dexmedetomidine yielded additive analgesic effect (Karadas *et al.*, 2007).

The aim of this study was to compare the analgesic effect of intraperitoneal dexmedetomidine or meperidine combined with bupivacaine to intraperitoneal bupivacaine alone in female patients undergoing elective laparoscopic gynecologic surgery.

MATERIALS AND METHODS

After approval of Local Ethical and Research Committee in Dar Alshifa hospital (in The State of Kuwait) during the period from January 2007 to December 2007, the informed written consents were obtained from sixty female patients (25-40 yeas old), ASA physical status 1 and 2 undergoing elective laparoscopic gynecologic surgery (e.g., diagnostic laparoscopy, adhesolysis, tubal ligation, ovarian cystectomy, etc.). Patients with previous abdominal surgery, hypertension, diabetic and cardiac patients were excluded from the study. Leaving intra-abdominal drain at the end of surgery was also a ground cause for exclusion. All patients were premedicated with oral midazolam 5 mg, approximately 60-90 min prior to surgery. Upon arrival to an operating room, a wide bore intravenous cannula was inserted and 8 mL kg^{-1} normal saline was infused intravenously. Electrocardiogram (lead 2 and 5 with ST segment analysis), pulse oximetry and non-invasive arterial blood pressure were monitored. Anesthesia was induced in all patients with intravenous 1.5 µg kg^{-1} fentanyl, 3-4 mg kg^{-1} propofol and 0.6 mg kg^{-1} rocuronium. The trachea was intubated with oral cuffed tube lubricated with lidocaine jelly 2%, 1-2 min after rocuronium administration guided by peripheral nerve stimulator. Intravenous lidocaine 2% (1 mg kg^{-1}) was injected one minute before endotracheal intubation. Ventilation was controlled using O_2/N_2O (50%:50%) with sevoflurane 1-1.5%. Nasogastric tube was inserted and end-tidal (Et) CO_2 was monitored after intubation. Ventilation was adjusted to maintain normocapnic ($EtCO_2$ around 36 mm Hg). Additional doses of rocuronium were given guided by peripheral nerve stimulation. Intravenous 10 mg metoclopramide, as well as intramuscular 75 mg diclofenac sodium were given following intubation in all patients. Diagnostic laparoscopy was done prior to proceeding to the surgical procedure. Surgery was conducted in the lithotomy and Trendelenberg position. Complete revision of hemostasis was done. Patients were randomly allocated (using table of randomization) into one of three equal sized groups (n = 20):

- **Group (B):** Intraperitoneal 50 mL bupivacaine 0.25% (125 mg) (Marcaine, Astra Zeneca)
- **Group (B+M):** Intraperitoneal 50 mL bupivacaine 0.25% (125 mg)+1 mg kg^{-1} meperidine
- **Group (B+D):** Intraperitoneal 50 mL bupivacaine 0.25% (125 mg)+1 µ kg^{-1} dexmedetomidine (Precedex®, Abbott Laboratories Inc., Abbott Park, IL)

The drugs were prepared and given to the investigator who was blinded to the identity of drugs.

In the three studied groups, at the end of surgery, intraperitoneal injection was guided by the camera on the surgical site and under both copulae of the diaphragm. Pain was assessed using Visual Analogue Scale (VAS), where zero score corresponds to no pain and 10 to the maximum or worst pain. Postoperative pain (VAS>3) was

initially managed with a bolus of 1 mg i.v. morphine. Patients were then instructed to start using intravenous Patient-Controlled Analgesia (PCA) morphine pump (IVAC 5000). The PCA pump was adjusted to deliver morphine boluses in 1 mg increments with a lockout interval of 10 min and a maximum hourly dose of 5 mg. The PCA regimen was reviewed if analgesia proved to be inadequate.

The following parameters were evaluated in all studied groups:

- Time to first request of analgesia (time elapsed between extubation and first request for analgesic dose)
- The amount of postoperative PCA morphine consumed in 0-6, 6-12, 12-18, 18-24 and 0-24 h following extubation
- The incidence and severity of postoperative shoulder and arm pain for 24 h (the severity of postoperative shoulder and arm pain measured at 1, 6, 12, 18 and 24 h, postoperatively, using (VAS)

Statistical analysis: All data were presented as mean (SD) or as median and range, comparison among groups was done using Analysis of Variance test (ANOVA) and post hoc test was performed in case of significant difference. Significance was considered where (p>0.05.) Statistical analysis was performed using the statistical computer program SPSS version 2.

RESULTS

Patient characteristics and operative details showed no significant differences among the three studied groups (Table 1).

Times to first request of postoperative analgesia were 45(10) min, 116 (20) min and 120 (18) min in groups (B), (B+M) and (B+D), respectively. It was significantly shorter in group (B) compared to the other 2 groups (p<0.05) with non significant difference between the later two groups ((B+M) and (B+D)) (Table 2).

Doses of intravenous PCA morphine consumed at 0-6, 6-12, 12-18, 18-24 and 0-24 h were significantly less in groups (B+M) and (B+D) compared to group (B) (p<0.05), with no significant difference between groups (B+M) and (B+D) (Table 2).

The incidence of shoulder pain were less in groups (B+M) and (B+D)) compared to group (B) (p<0.05) with no significant difference between groups (B+M) and (B+D) (Table 2).

The severity of shoulder pain measured at 1, 6, 12, 18 and 24 h were significantly less in groups (B+M)

Table 1: Patient characteristics and operative data in the studied groups (mean±SD)

Parameters	Group (B) (n = 20)	Group (B+M) (n = 20)	Group (B+D) (n = 20)
Age (years)	30±2	29±1	31±2
Weight (kg)	82±3	84±4	81±2
Height (cm)	173±3	169±2	170±2
Duration of surgery (min)	56±2	61±3	56±3

B: Bupivacaine, D: Dexmedetomidine, M: Meperidine, No significant differences among the studied groups

Table 2: Postoperative analgesic requirements, time to first request of analgesia (mean±SD) and incidence of postoperative shoulder pain (number (%) of patients)

Parameters	Group (B) (n = 20)	Group (B+M) (n = 20)	Group (B+D) (n = 20)
Time to first request of postoperative morphine (min)	45±10	116±20*	120±18*
Dose of morphine (mg) at			
0-6 h	6±1	3±0.3*	3±0.5*
6-12 h	6±1	4±0.5*	3±0.6*
12-18 h	7±1	3±0.2*	4±0.5*
18-24 h	6±1	4±0.2*	3±0.4*
0-24 h	24±1	13±2.0*	12±1.0*
Incidence of postoperative shoulder pain	15 (75%)	7 (035%)*	6 (30%)*

B: Bupivacaine, D: Dexmedetomidine, M: Meperidine, *Significantly different (p<0.05) compared to group (B)

Table 3: Postoperative Visual Analogue Scale (VAS from 0 to 10) for patients in the studied groups (median (range)

Time (h)	Group (B) (n = 20)	Group (B+M) (n = 20)	Group (B+D) (n = 20)
1	5 (4-7)	4 (3-7)*	3 (3-5)*
6	6 (5-7)	3 (3-6)*	4 (3-6)*
12	7 (5-8)	4 (3-6)*	3 (2-6)*
18	6 (4-7)	3 (3-5)*	3 (3-6)*
24	5 (4-7)	4 (2-6)*	4 (3-7)*

B: Bupivacaine, D: Dexmedetomidine, M: Meperidine, *Significant difference (p>0.05) compared to group (B)

and (B+D) compared to group (B) (p<0.05) with no significant difference between groups (B+M) and (B+D) (Table 3).

DISCUSSION

Patients undergoing laparoscopic surgery tend to expect a painless postoperative period because of common beliefs about this type of surgery. However, pain after laparoscopic surgery is still one of the important postoperative problems. Almost 80% of patients need opioid analgesia in the postoperative period (Karadas *et al.*, 2007; Colbert *et al.*, 2000)

The rationale for intraperitoneal administration of drugs for treatment of the pain which follows laparoscopic surgery is that the small incisions at the abdominal wall cause the visceral component of the pain to be more prominent. With this in mind, many authors have tried to diminish pain via the peritoneal route. The intraperitoneal technique using bupivacaine or meperidine

in laparoscopic surgery is deemed to be safe, improve patient comfort, shorten the length of stay in the postoperative care unit and decrease the requirement for nursing care in the ward (Karadas *et al.*, 2007; Colbert *et al.*, 2000).

In the present study, the results has shown that combination of meperidine 1 mg kg^{-1} and bupivacaine (0.25%) was superior to bupivacaine (0.25%) alone when installed intraperitoneally as regards the time to first request for analgesia, the dose of morphine consumed and the postoperative pain.

These results were in agreement with those of the study done by Colbert *et al.* (2000), who studied the analgesic effect of adding 50 mg meperidine to intraperitoneal bupivacaine in post-laparoscopic tubal ligation.

In disagreement with results of present study, the study done by Michael *et al.* (2008), concluded that; Compared with systemic opioid, IP meperidine and ropivacaine, alone or in combination, did not produce better pain relief or opioid dose-sparing after laparoscopic surgery.

The discrepancy between their results and the present study may be attributed to the population of the study as regards the type of laparoscopic surgery which was not confined to gynaecologic (lower abdominal) surgery.

To our knowledge, there was no clinical study in the literature examined the analgesic effect of dexmedetomidine intraperitoneally in human but intraperitoneal clonidine (another an α-2 agonist) was studied by Memis *et al.* (2005).

The present study demonstrated that intraperitoneal administration of dexmedetomidine (1 μ kg^{-1}) in combination with bupivacaine 0.25% (125 mg) compared to bupivacaine 0.25% (125 mg) alone was associated with reduction of shoulder pain, values of postoperative VAS, postoperative analgesic requirements and increased time to the first request of postoperative morphine.

In agreement with the results of the present study was study done by Memis *et al.* (2005) which has shown that combination of intraperitoneal bupivacaine 0.5% with either clonidine 1 μ kg^{-1} or tramadol 100 mg gave more effective analgesia than bupivacaine alone in the early postoperative period in total abdominal hysterectomy patients and the study done by Karadas *et al.* (2007), on rats, who found that combination of topical COX-2 inhibitors with intraperitoneal dexmedetomidine yielded additive analgesic effect and The antinociceptive effect of dexmedetomidine was blocked by systemic pretreatment of selective α^2-adrenoceptor antagonist, atipamezole.

In disagreement with results of the present study, the study done by Schulte Steinberg *et al.* (1995), who found intraperitoneal bupivacaine (0.25%) was ineffective as analgesic after laparoscopic cholecystectomy and attributed the lack of effect of intraperitoneal injections to the small dose and to a rapid dilution within the peritoneal cavity.

The discrepancy between these results and present study may explained by the big difference in the volume of local anesthetic injected in the peritoneal cavity being 50 mL in the present study and only 20 mL in the study of Schulte Steinberg *et al.* (1995).

Regarding the postoperative analgesic requirement, the present study has shown statistically significant higher doses of postoperative morphine requirement in Bupivacaine Group (B) compared to the other two groups, which were comparable (p>0.05).

But the results of the study done by Memis *et al.* (2005), found that, when tramadol or clonidine was added to intaperitoneal bupivacaine, compared to bupivacaine alone, a higher statistically significance postoperative analgesic requirement with tramadol than clonidine, but still the postoperative analgesic requirement in bupivacaine alone group was higher than the other two groups. The more prominent effect of the α-2 agonist in the present study may be attributed to the difference in potency of the drug generation (Dexmedetomidine) in the present study and (Clonidine) in Memis *et al.* (2005), study.

The results of the present study has shown a statistically significant delayed time for the first postoperative analgesic requirement in (Bupivacaine + Meperidine) groups and (Bupivacaine +Dexmedetomidine) group compared to (Bupivacaine) group, (110 (20) min, 120 (18) min and 45 (10) min, respectively).

This was also in agreement with the study done by Memis *et al.* (2005) where their results were close to the results of the present study.

Esmaoglu *et al.* (2005) studied the addition of dexmedetomidine to lidocaine for intravenous regional anesthesia and their results were in parallel with those of the present study regarding the intensity of analgesia, the time for the first postoperative analgesic requirement and its total dose. Meanwhile they noticed no significant difference between the groups with respect to sensory and motor blocks (onset and regression time), which may attributed to the rapid onset of lidocaine.

We conclude that intraperitoneal instillation of dexmedetomidine (1 μ kg^{-1}) or meperidine (1 mg kg^{-1}) in combination with bupivacaine 0.25% (125 mg) in female patients undergoing laparoscopic gynecologic surgery significantly decreases the postoperative analgesic requirements of intravenous morphine and decreased the incidence of shoulder pain compared to intraperitoneal bupivacaine 0.25% (125 mg) alone.

REFERENCES

Alhashemi, J.A., 2006. Dexmedetomidine vs midazolam for monitored anaesthesia care during cataract surgery. Br. J. Anesth., 96: 722-726.

Colbert, S.T., K. Moran, O.D.M. Hanlon, F. Chambers, D.C. Moriarty and W.P. Blunnie, 2000. An assessment of the value of intraperitoneal meperidine for analgesia postlaparoscopic tubal ligation. Anesth. Analg., 91: 667-670.

Esmaoglu, A., A. Mizrak, A. Akin, Y. Turk and A. Boyaci, 2005. Addition of dexmedetomidine to lidocaine for intravenous regional anaesthesia. Eur. J. Anaesthesiol., 22: 447-451.

Hedayati, B. and S. Fear, 1999. Hospital admission after daycase gynaecological laparoscopy. Br. J. Anaesth., 83: 776-779.

Karadas, B., T. Kaya, S. Gulturk, A. Parlak, S. Gursoy, A. Cetin and I. Bagcivan, 2007. Additive interaction of intraperitoneal dexmedetomidine and topical nimesulide celecoxib and DFU for antinociception. Eur. J. Pharmacol., 556: 62-68.

Kazama, T., K. Ikeda, T. Kato and M. Kikura, 1996. Carbon dioxide output in laparoscopic cholecystectomy. Br. J. Anaesth., 76: 530-535.

Lee, I.O., S.H. Kim, M.H. Kong, M.K. Lee, N.S. Kim, Y.S. Choi and S.H. Lim, 2001. Pain after laparoscopic cholecystectomy: The timing of incisional and intraperitoneal bupivacaine. Can. J. Anesth., 48: 545-550.

Lujan, J.A., M.D. Frutos and Q. Hernandez *et al.*, 2004. *Laparoscopic versus* open gastric bypass in the treatment of morbid obesity: A randomized prospective study. Ann. Surg., 239: 433-437.

Memis, D., A. Turan, B. Karamanlioglu, B. Tükenmez and Z. Pamukçu, 2005. The effect of tramadol or clonidine added to intraperitoneal bupivacaine on postoperative pain in total abdominal hysterectomy. J. Opioid. Manage., 1: 77-82.

Michael, J.P., K.F. Ilett, P.L. Hackett, M. Page-Sharp and R.W. Parsons, 2008. Disposition and clinical outcome after intraperitoneal meperidine and ropivacaine administration during laparoscopic surgery. Anesth. Analg., 106: 278-286.

Nilsson, G., S. Larsson and F. Johnsson, 2000. Randomized clinical trial of laparoscopic versus open fundoplication: Blind evaluation of recovery and discharge period. Br. J. Surg., 87: 873-878.

Schulte Steinberg, H., E. Weninger, D. Jokisch, B. Hofstetter, A. Misera, V. Lange and C. Stein, 1995. Intraperitoneal versus interpleural morphine or bupivacaine for pain after laparoscopic cholecystectomy. Anesthesiology, 82: 634-640.

Tanskanen, P.E., J.V. Kyttä, T.T. Randell and R.E. Aantaa, 2006. Dexmedetomidine as an anaesthetic adjuvant in patients undergoing intracranial tumour surgery: A double-blind, randomized and placebo-controlled study. Br. J. Anaesth., 97: 658-665.

Visalyaputra, S., N. Pethpaisit and P. Ariyanon *et al.*, 2002. EMLA cream and intraperitoneal lidocaine decrease intraoperative pain during postpartum tubal sterilization. J. Med. Assoc. Thai., 85: S942-S947.