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REGIONAL ANAESTHESIA

Postoperative analgesic effect of intravenous (i.v.) clonidine compared with clonidine administration in wound infiltration for open cholecystectomy[†]

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Editor's key points

- Optimal postoperative pain control with minimal side-effects is a good clinical target.
- Clonidine is a widely available α_2 agonist for perioperative analgesia, but its ideal route of administration is unclear.
- I.V. clonidine and local infiltration both provided good analgesia, with more side-effects in the i.v. group.

Objectives. This randomized double-blind study was designed to compare the postoperative analgesic effect of clonidine administered intravenously or in wound infiltration with bupivacaine.

Methods. Sixty adults of ASA grade I–II undergoing open cholecystectomy were randomly allocated into three groups. Group 1 (control group) patients received wound infiltration with 30 ml of 0.25% bupivacaine at the end of surgery. Group 2 patients received 3 μg kg^{-1} clonidine intravenously after resection of gall bladder plus wound infiltration with 30 ml of 0.25% bupivacaine. Group 3 patients received wound infiltration with 3 μg kg^{-1} clonidine with 30 ml of 0.25% bupivacaine. A standard general anaesthesia technique was used. Postoperative analgesia was provided with i.v. diclofenac and morphine on demand. Postoperative pain, number of patients requiring rescue analgesia and total morphine consumption during 24 h after operation was recorded.

Results. Postoperative morphine consumption was significantly less in patients receiving clonidine by either route when compared with the control group ($P<0.0001$). All patients in the control group required supplemental morphine, with nine patients in the i.v. clonidine group and 11 patients in the wound infiltration group ($P<0.002$). Pain scores were lower at rest for 12 h and on cough for 6 h in both clonidine groups when compared with the control group ($P<0.01$). Patients receiving i.v. clonidine had more hypotension ($P<0.01$) and sedation ($P<0.001$) compared with other groups.

Conclusions. Clonidine 3 μg kg^{-1} provided effective postoperative analgesia and reduced morphine requirement when administered intravenously or in wound infiltration with bupivacaine. However, the incidence of complications was less with wound infiltration.

Clinical trial registry of India: (www.ctri.nic.in/), registration number CTRI/2012/12/003258.

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Acute postoperative pain after upper abdominal surgeries, like open cholecystectomy, may delay patient recovery and discharge from hospital.[1] A multimodal approach, using a combination of opioid and non-opioid analgesics improved the quality of postoperative analgesia and reduced adverse effects.[2]

Clonidine, an α_2-adrenoceptor agonist, has potent antinociceptive properties.[3] However, the therapeutic utility of systemic clonidine for treatment of pain is limited by its centrally mediated side-effects including sedation, hypotension, and rebound hypertension.[4] A peripheral analgesic action of clonidine has been suggested after topical application in the treatment of sympathetic pain[5] and after intra-articular administration in preclinical[6] and clinical studies.[7][8] A few studies have used clonidine infiltration at the surgical site with conflicting results.[9][10] Pre-incisional injection of clonidine with ropivacaine in the tonsillar fossae was found to be effective in decreasing postoperative analgesic consumption and pain scores.[9] However, in another study, clonidine

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administration with bupivacaine in wound infiltration did not improve postoperative analgesia obtained by bupivacaine alone for elective inguinal hernia repair.[10] The primary objective of this study was to determine the analgesic efficacy of clonidine in wound infiltration with bupivacaine and to compare it with i.v. administration for postoperative analgesic requirement and side-effects in patients undergoing open cholecystectomy.

Methods

The study was approved by 'Institutional Ethics Review Committee' (Ref.: MS/843/MD7818). The clinical trial is also registered with 'clinical trial registry of India' (www.ctri.nic.in/) and the registration number for this trial is *CTRI/2012/12/003258*. Sixty patients of ASA physical status I–II, in the age group of 18–60 yr, listed for elective open cholecystectomy were selected. Patients with morbid obesity, Reynaud's disease or hepato-renal insufficiency, receiving adrenoreceptor agonists, antagonists, or narcotics before operation were excluded. All patients underwent a preoperative assessment on the day before surgery and written informed consent was obtained for participation in the study. They were premedicated with oral diazepam 0.1 mg kg^{-1} at night and 2 h before surgery.

Patients were randomly allocated into three groups by using a computer generated random number table. Group 1 (control group) patients received 100 ml normal saline before closure plus wound infiltration with 30 ml of 0.25% bupivacaine at the end of surgery. Group 2 patients received clonidine 3 μg kg^{-1} in 100 ml normal saline infusion over 10 min before closure plus wound infiltration with 30 ml of 0.25% bupivacaine at the end of surgery. Group 3 patients received 100 ml normal saline before closure plus wound infiltration with 3 μg kg^{-1} clonidine added to 30 ml of 0.25% bupivacaine at the end of surgery. The person who prepared the study drugs did not participate in the data collection.

Anaesthesia was induced with propofol 2–3 mg kg^{-1} and morphine 0.1 mg kg^{-1}. Tracheal intubation was facilitated by vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained by isoflurane and 66% nitrous oxide in oxygen. Patients were monitored using Datex-Ohmeda S5 Avance work station. Intraoperative monitoring included electrocardiogram (lead II and V5), non-invasive arterial pressure (at 5 min intervals), oxygen saturation, end-tidal carbon dioxide, and nasopharyngeal temperature. Patients' lungs were ventilated by intermittent positive pressure ventilation using a circle system to maintain normocapnia. A continuous infusion of normal saline was given at the rate of 5–8 ml kg^{-1} during surgery. Heart rate and mean arterial pressure (MAP) were maintained within 20% of the preoperative value. Hypotension (MAP<20% of baseline or <60 mm Hg) was treated with infusion of normal saline and if required injection mephentermine 3–6 mg boluses. Bradycardia (heart rate <40 beats min^{-1}) was treated with atropine 40 μg kg^{-1} bolus. All patients received i.v. diclofenac 1.5 mg kg^{-1} and ondansetron 0.1 mg kg^{-1} half an hour before the completion of surgery. At the end of surgery, residual neuromuscular block was reversed with

neostigmine and glycopyrrolate. Tracheal extubation was performed on meeting the standard criteria for extubation.

The patients were observed for 24 h after operation in the post-anaesthesia care unit (PACU) by an anaesthesiologist who was not aware of the patients' group assignment. Postoperative analgesia was provided with i.v. diclofenac 1.5 mg kg^{-1} every 8 h. The pain at rest and on cough was assessed by visual analogue scale (VAS, 0–10, 0=no pain, 10=maximum imaginable pain) at the time of arrival in PACU and then after 2, 4, 6, 12, and 24 h after operation. Rescue analgesia was given with i.v. morphine 3 mg boluses on demand or whenever VAS pain score was ≥4. The number of patients requiring rescue analgesia and total morphine consumption during the first 24 h after operation was recorded. The level of sedation was assessed by using four-point sedation scale [0–3, 0=awake and oriented, 1=drowsy but responding to command, 2=sleepy but easy to arouse (by loud command or glabellar tap), 3=deep sleep, difficult to arouse]. The incidence and severity of nausea was assessed by four-point categorical scale (0=none, 1=mild, 2=moderate, and 3=severe). I.V. metoclopramide 10 mg was given for severe nausea or vomiting. Any other adverse events like hypotension, bradycardia, dry mouth, dizziness, and diplopia were also recorded. Patients' satisfaction with the technique was assessed at 24 h after operation on an 11-point satisfaction score (0=unsatisfied, 10=most satisfied).

Statistical analysis

Statistical significance for analgesic requirement was determined by one-way analysis of variance (ANOVA). The pain scores, sedation scores, and patient satisfaction scores (non-parametric data) were compared by Kruskal–Wallis ANOVA followed by Mann–Whitney *U*-test for intergroup differences. ASA physical status, sex ratio, and need for rescue analgesia in recovery room were analysed using χ^2-test and Fisher's exact test. Bonferroni correction was used for multiple comparisons. Comparisons of heart rate and arterial pressure were made using ANOVA, followed by Student–Neumans–Keul test for in-between group comparisons. Differences were considered significant if *P*<0.05. Sample size was calculated on the basis of previous study.[11] At 95% significance level and 80% power, assuming 30% reduction in morphine consumption, 17 patients were required in each group. To minimize the effects of data loss a total of 60 patients were enrolled.

Results

In total, 56 patients completed the study out of 60 recruited (Fig. 1). Four patients were excluded from the analysis (two patients had high arterial pressure before induction and two patients underwent laparotomy because of common bile duct stone). All the groups were similar with respect to patient characteristic data, ASA physical status and duration of surgery (Table 1). Intraoperative heart rate and MAP were comparable among groups.

Patients receiving clonidine by either route had significantly lower pain scores at rest for 12 h and on cough for
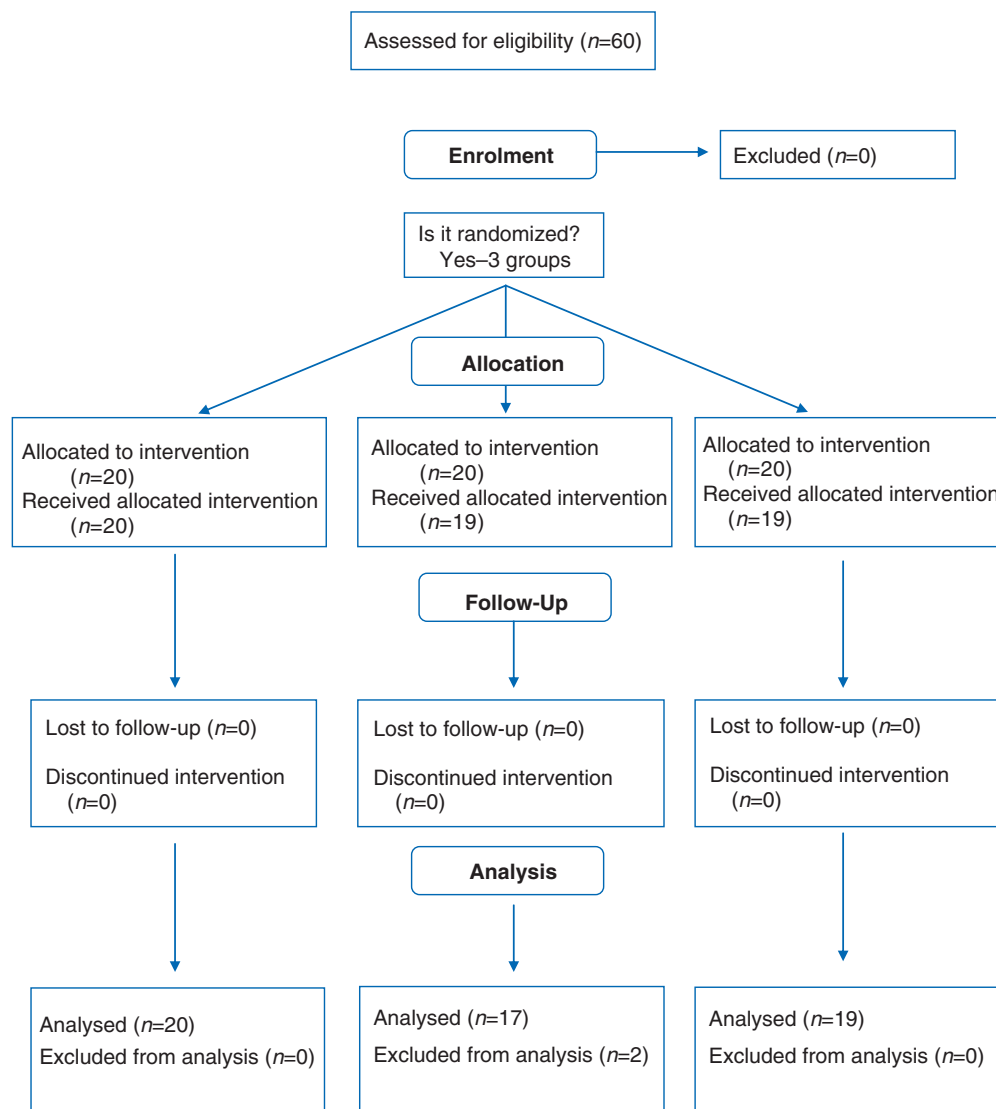
Fig 1 CONSORT diagram.

Table 1 Patients characteristics and duration of surgery [number, mean (range) and mean (SEM)]. WI, wound infiltration

Variables	Group 1 (control) (n=20)	Group 2 (clonidine i.v.) (n=17)	Group 3 (clonidine WI) (n=19)
Age (yr)	47.4 (34–65)	50.5 (40–66)	50.8 (42–70)
Weight (kg)	61.8 (10.1)	58.7 (11.7)	55.2 (9.6)
Sex ratio (M:F)	14:6	13:4	14:5
ASA (I:II)	15:5	14:3	16:3
Duration of surgery (min)	68.75 (17.08)	71.25 (22.76)	72.75 (20.96)

6 h after operation when compared with patients who received bupivacaine alone (Fig. 2). The 24 h morphine consumption was also less in both clonidine groups when compared with the control group (Table 2). All patients in the control group required supplemental morphine; while only nine patients in the i.v. clonidine group and 11 patients in the wound infiltration group did (Table 2). The difference in the pain scores and morphine consumption was not significant between i.v. and wound infiltration clonidine groups.

Sedation scores were significantly higher for 2 h after operation in the i.v. clonidine group (median, IQR=2.00, 1) when compared with the control group (median, IQR=1.00, 0, $P<0.001$) and wound infiltration group (median, IQR=2.00, 0, $P<0.01$). The incidence of postoperative hypotension was also high in the i.v. clonidine group when

compared with the other two groups ($P<0.01$). Six patients developed hypotension in the i.v. clonidine group while one patient in the control group and two patients in the infiltration group did. One patient in each group had severe nausea or vomiting and required parenteral metoclopramide. No other side-effect was recorded in any group of patients. Patients receiving clonidine by either route were more satisfied than the control group [satisfaction score, median (IQR), 6.00 (1), 8.00 (0), 8.00 (1) for Groups 1, 2, and 3, respectively, $P<0.0001$].
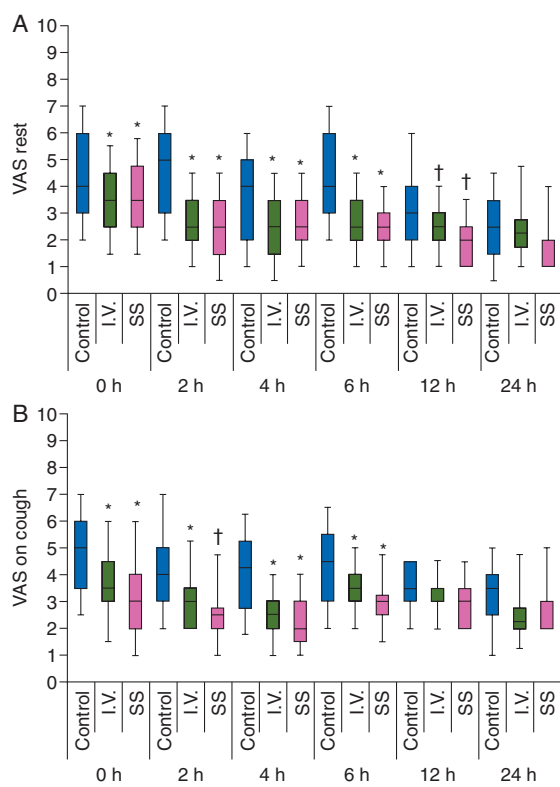
Discussion

Surgical wound infiltration with local anaesthetic agents is a cost-effective and relatively low-risk method for providing postoperative analgesia after orthopaedic, general, and

Fig 2 VAS (A) at rest and (B) on cough. Boxes indicate median with 25th and 75th percentiles and whisker caps indicate 10th and 90th percentiles. Control, Group 1; I.V., Group 2; SS, Group 3 (*$P<0.01$ compared with Group 1; †$P<0.05$ compared with Group 1).

gynaecological surgeries.[12–14] The duration of analgesia can be prolonged by addition of various adjuvants such as epinephrine, ketorolac, and an opioid.[15 16] Various preclinical and clinical studies have reported that clonidine produces potent antinociception regardless of the root of administration (central or peripheral).[6–9] However, few clinical reports could not demonstrate the analgesic effect of clonidine after local as well as administration.[10 17]

In the present study, patients who received clonidine either in wound infiltration with bupivacaine or by i.v. route had reduced postoperative pain scores and morphine requirement when compared with the control group. The cumulative 24 h morphine consumption was reduced by $>50\%$ in patients receiving clonidine by either route compared with the control group ($P<0.0001$).

Clonidine has been shown to provide effective analgesia when administered into the knee joint after arthroscopy.[7 8] Giannoni and colleagues[9] found that peritosillar infiltration of clonidine 1 μg kg^{-1} along with ropivacaine significantly reduced the requirement of postoperative fentanyl and codeine ($P<0.05$). Patients who received clonidine with ropivacaine had lower pain scores on the fifth postoperative day compared with patients who received ropivacaine alone ($P<0.05$). The incidence of otalgia was also lower in the ropivacaine clonidine treated group compared with the control group.[9] While in another study, Connelly and colleagues[17] reported an improvement in postoperative analgesia for only 2 h after surgical site infiltration or i.m. administration of clonidine 0.5 μg kg^{-1} in patients undergoing inguinal hernia repair under monitored anaesthesia care. The authors stated utilizing higher concentrations of clonidine (>0.5 μg kg^{-1}) might be necessary to enhance the analgesic effect.[17] Elliot and colleagues[10] could not find any significant difference in postoperative analgesic consumption after i.m. administration or wound infiltration of clonidine (150 μg) in patients undergoing inguinal herniorrhaphy. All patients received 29 ml of 0.25% bupivacaine infiltration in a three-stage technique: along the line of incision, through the external oblique apponeurosis, and direct infiltration to block ilio-inguinal and iliohypogastric nerves. As stated by the authors, a possible reason for negative findings in their study might be that any extension of pharmacological action of local anaesthetic by clonidine would have been concealed by the prolonged analgesia provided by the block itself.

Though, the precise mechanism of topical clonidine analgesia remains unclear, several lines of evidence support this contention.[18] It has been suggested that sympathetic neural activity and norepinephrine have an excitatory effect on

Table 2 Postoperative morphine requirement [mean (SEM) and number (%)]. i.v., intravenous; WI, wound infiltration. *$P<0.05$ between Groups 1 and 2; †$P<0.05$ between Groups 1 and 3

Variables	Group 1 (control) ($n=20$)	Group 2 (clonidine i.v.) ($n=17$)	Group 3 (clonidine WI) ($n=19$)	*P*-value
Total morphine consumption (mg)	9.3 (2.36)*,†	1.95 (2.01)	2.4 (2.5)	0.00
Patients requiring morphine	20 (100)*,†	9 (53)	11 (58)	0.002

nociceptive discharge after cutaneous injury.[19] Because clonidine inhibits the release of norepinephrine from prejunctional α_2-adrenoreceptors in the periphery, it may potentially inhibit neural activity in nociceptive pathways.[20] Other proposed mechanisms include enhancing the effect of local anaesthetics by selectively blocking conduction of $A\delta$ and C fibres, and release of enkephalin like substances which produce a peripheral analgesic effect.[3]

Clonidine produces dose dependent analgesia and adverse effects on parenteral administration.[11 21 22] In a dose–response study, Mariangeli and colleagues[21] demonstrated that i.v. clonidine 3 μg kg^{-1} was more effective than clonidine 2 μg kg^{-1} for postoperative pain relief after hemilaminectomy, while clonidine 5 μg kg^{-1} resulted in similar analgesia with significant side-effects. Hypotension and sedation are the common side-effects of clonidine on parenteral administration. Elliot and colleagues[10] found a higher incidence of hypotension ($\sim$13%) in patients who received i.m. clonidine compared with wound infiltration and control groups. In our study, the incidence of hypotension and sedation was more in patients who received i.v. clonidine but not in wound infiltration. Dogrul and colleagues[23] demonstrated that topical administration of clonidine elicits antinociception by blocking the emerging pain signals at peripheral terminals through α_2-adrenoreceptors without producing the undesirable central side-effects observed after systemic administration.

The limitation of our study is that we could not follow-up the patients after 24 h as patients were discharged on the next day. We selected the patients undergoing open cholecystectomy which has limited indications at present. Although it is a small surgical procedure and requires a short-time admission, the acute postoperative pain after open cholecystectomy may delay discharge of the patient from hospital.

In conclusion, clonidine when administered in wound infiltration with bupivacaine provides effective postoperative analgesia as on i.v. administration but had fewer side-effects. Therefore, clonidine 3 μg kg^{-1} with bupivacaine can be used for surgical site infiltration as part of a multimodal analgesia technique in patients undergoing open cholecystectomy. However, further studies are required to evaluate its efficacy in different surgical procedures.

Declaration of interest

None declared.

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