

## Comparison of intrathecal and intravenous clonidine on attenuating haemodynamic response to capnoperitoneum

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**Background and aims:** Clonidine has been used via different routes to suppress the haemodynamic stress responses associated with capnoperitoneum. This study was designed to compare the stress response attenuating effect of equal doses of intrathecal (IT) and intravenous (IV) clonidine during capnoperitoneum under general anaesthesia.

**Method:** Seventy-five patients satisfying inclusion criteria were randomly allocated to three groups of 25 patients each. Group C-IV patients received 1µg/kg i.v. clonidine, 15mins before induction. Group C-IT patients received the same dose intrathecally just before induction. Group N was the control group. Intraoperative haemodynamic parameters, post-operative pain and sedation were assessed. Patients requiring nitroglycerine (NTG) to maintain mean arterial pressure (MAP) below 20% of baseline were noted.

**Results:** There was a statistically significant difference ( $p=0.04$ ) in the number of patients who required NTG between group C-IT and group C-IV [0% vs 16% ( $p=0.04$ )] and between group C-IT and group N [0% vs 36% ( $p=0.001$ )]. Rescue analgesia was required in 16 patients in group C-IV, 10 patients in group C-IT and 20 patients in group N in the first two hours after surgery. None of the patients in either group were deeply sedated at tracheal extubation.

**Conclusion:** At 1µg/kg, IT clonidine is more effective than IV clonidine in suppressing haemodynamic stress response to capnoperitoneum. Both IT and IV clonidine provide early post-operative analgesia without causing much sedation.

**Keywords:** Laparoscopy; physiological stress; clonidine; spinal anaesthesia

### Introduction

Capnoperitoneum during laparoscopy causes significant haemodynamic changes.<sup>1-4</sup> Pharmacological agents like  $\beta$ -blockers, opioids, nitroglycerine and dexmedetomidine have been used to minimize such derangements with varied results.<sup>5-9</sup> Nitroglycerine (NTG) is commonly used as a rescue measure for intraoperative hypertension.<sup>10,11</sup> Clonidine, an  $\alpha$ -2 adrenoceptor agonist, reduces sympathetic outflow and is advantageous in laparoscopic procedures.<sup>12</sup> In addition,  $\alpha$ -2 agonists also induce analgesia by acting at different sites; the brain, brain stem, spinal cord and peripheral nerves.<sup>13</sup>

Clonidine can be administered via various routes [oral, intramuscular (IM), intravenous (IV), intrathecal (IT), epidural] and used in doses ranging from 1 – 8µg/kg.<sup>14-17</sup> At equal doses, IT clonidine has been shown to produce better analgesia than IV clonidine.<sup>18</sup> The effect of IT clonidine on maintaining haemodynamic stability during laparoscopic procedures has not been studied so far. This study was designed to compare the stress response attenuating effect of equal doses of IT and IV clonidine during capnoperitoneum. Our primary objective was to assess the number of patients requiring NTG to maintain mean arterial pressure (MAP) within 20% of baseline. Secondary objectives were to assess the post-operative pain and sedation.

### Methodology

After approval from the Institutional Ethics Committee (PG/2014/122), this randomized prospective observer blinded study was conducted at a tertiary care hospital from

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January 2015 to July 2016. American Society of Anaesthesiologists (ASA) physical status 1 and 2 patients, between the age group 18 –65years admitted for laparoscopic surgeries (cholecystectomy, appendectomy, diagnostic laparoscopy) under general anaesthesia (GA) formed the study population.

After pre-anaesthetic assessment, 75 patients were selected from study population using a random table. Written informed consent for participation was obtained. Exclusion criteria were patient refusal for spinal, expected pneumoperitoneum duration less than 60mins, laparoscopic surgeries requiring steep head low or head up positions, A-V conduction block, HR <55beats/min, hypertensive patients and any other absolute contraindications for spinal anaesthesia.

All patients who participated in the study were kept nil per oral for a period of at least 6hrs for solids and 2hrs for clear fluids. They were pre-medicated with alprazolam 0.5mg and ranitidine 150mg per oral on the night before surgery and morning of surgery. On the day of surgery, an 18G IV cannula was secured and preloading with 500ml of Ringer Lactate solution was done in the pre-operative holding area. Midazolam 0.02mg/kg was administered IV. Patients were randomized by an independent person to either IV clonidine (C-IV), IT clonidine (C-IT) or control (N) group by sealed envelope technique. Baseline blood pressure and HR were recorded in the pre-operative holding area, before administration of the study drug.

In the C-IV group, 1µg/kg clonidine hydrochloride (Cloneon, Neon laboratories) was administered diluted in 100ml normal saline over 15mins in the pre-operative holding area under standard monitoring. (Figure 1) After infusion, patients were shifted to operation theatre (OT) and GA was induced. In the C-IT group, 1µg/kg (maximum of 75µg) preservative free clonidine was given in L3-L4 interspace diluted with 1.5ml cerebrospinal fluid (CSF), following which GA was administered.

In OT, monitoring (GE S5 Anaesthesia monitor, GE Healthcare, United States) included electrocardiography, pulse oximetry, non-invasive blood pressure, minimal alveolar concentration (MAC) of anaesthetic agent, EtCO<sub>2</sub> and train of four (TOF) (Organon Ltd. Ireland) for neuromuscular blockade.



**Figure 1:** Clonidine hydrochloride

After pre-oxygenating with 6L/min of O<sub>2</sub> for 3mins, patients were induced with fentanyl 2µg/kg and propofol 2mg/kg. Vecuronium bromide 0.1mg/kg was administered, and patients were mask ventilated with 6 L/min flow using a mixture of 33% oxygen, 66% nitrous oxide (N<sub>2</sub>O) and 1.5% dial concentration of isoflurane for 3 minutes. Tracheal intubation was done when TOF count was 0. After confirmation of proper endotracheal tube placement, intermittent positive pressure ventilation was instituted, with tidal volume of 8ml/kg lean body mass and respiratory rate 12/min and adjusted to maintain EtCO<sub>2</sub> between 30-35mmHg. After 10 minutes on high flow, anaesthesia was maintained with 800ml fresh gas flow with O<sub>2</sub>, N<sub>2</sub>O ratio of 50:50 and 1.5% dial concentration isoflurane. Isoflurane was adjusted accordingly to maintain a minimum alveolar concentration (MAC) - of 1.0. During laparoscopy, intra-abdominal pressure (IAP) was maintained at 12mmHg. Haemodynamic parameters were recorded by a blinded observer before induction, before intubation, every 5mins after intubation, before carbon-di-oxide (CO<sub>2</sub>) insufflation and then every 5mins for 60mins of capnoperitoneum. Time of initiating and ending capnoperitoneum and end of surgery were also noted. Intermittent boluses of 0.02mg/kg vecuronium were administered when TOF count was 2. Fentanyl i.v. was repeated at doses of 0.5µg/kg every hour.

An increase in MAP beyond 20% of baseline value was managed with NTG infusion starting at 0.3µg/kg/min and titrated with 0.1µg/kg/min increments every 5mins till it was within limits. Once initiated, NTG was tapered and stopped only when MAP fell below the baseline MAP level. Any fall in systolic blood pressure (SBP) below 80mmHg or MAP below 60mmHg, was treated with 3mg boluses of mephenteramine. A decrease in HR to less than 50/min was treated with 0.3mg of i.v. atropine.

Isoflurane was stopped after deflating the abdomen and the ports were taken out. After application of dressing, reversal of neuromuscular blockade was done when TOF count was 2, following which N<sub>2</sub>O was stopped and fresh gas flows increased to 8L/min. Tracheal extubation was done when respiratory parameters were adequate, and patient was responding to oral commands. After tracheal extubation, pain and sedation were recorded at thirty-minute intervals for two hours. Pain was graded on a numeric pain rating scale of 0 to 10 and graded as no pain (0), mild pain (1-3), moderate pain (4-6) or severe pain (7-10). Paracetamol 1gm was administered i.v. when patient complained of moderate pain. Sedation was recorded on a five-point scale (0- Awake, agitated; 1- Awake, comfortable; 2- Asleep, arousable; 3- Asleep, sluggish response to command; 4- No response to verbal command or touch).<sup>10</sup>

The incidence of hypertension in laparoscopic surgeries has been reported to be 46.7% by.<sup>10</sup> Based on this study, sample size was calculated to detect a 40% reduction in the incidence of hypertensive response in C-IT group when compared to control group, with an alpha error of 0.05 and power of 80% using the formula  $n = (a+b)^2 [ p_1q_1 + p_2q_2 ] / x^2 [ a = 1.96, b = 0.842, p_1 = 46.7, q_1 = 53.3, p_2 = 18.68, q_2 = 81.3 ]$ . The sample size was calculated to be 19 patients in each group. Taking into account the drop outs, 25 patients were included in the study.

Sample size calculation: All data were entered into a Data Collection Proforma Sheet and were entered into Excel (MS Excel 2010). Statistical analysis was carried out using SPSS version 16.0 (IBM SPSS, US) software. Descriptive data were reported as mean ± standard deviation. Sex and ASA status was analyzed using Kruskal Wallis test. Age, duration of pneumoperitoneum and duration of surgery were analyzed using one-way ANOVA. Haemodynamic data were analyzed using repeated measures ANOVA with post-hoc test for comparison between the groups. Chi-square test was used for number of patients requiring NTG. Post-op pain and sedation was analyzed using Chi square test and Mann Whitney test.

**Results**

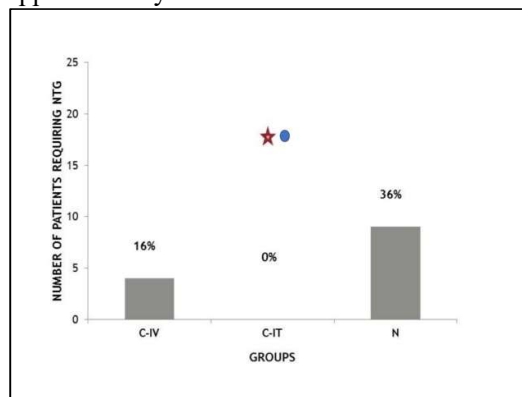
Seventy-five patients were enrolled in the study. They were randomized into three groups. The

groups were comparable in terms of age, sex distribution, ASA physical status, duration of pneumoperitoneum, duration of surgery and type of surgery (Table 1).

**Table 1:** Demographic data.

Parameter				P Value
	Group C-IV (n=25)	Group C-IT (n=25)	Group N (n=25)	
Age (Years)	36±12	32±10	36±10	0.385
Sex (M: F)	8:17	11:14	11:14	0.607
ASA (1:2)	13:12	12:13	14:11	0.852
Duration of pneumoperitoneum (Min)	72±13.69	71.18±11.16	71.8±21.3	0.999
Duration of surgery (Min)	90±19	86.60±13.5	88±22.5	0.813
Type of surgeries:				
Upper abdominal	5	4	5	0.623
Lower abdominal	20	21	20	0.718

In all patients MAP was maintained within 20% of baseline with NTG infusion as necessary. Requirement of NTG was 16% patients in group C-IV, 0 patients in group C- IT and 36% of patients in group N (Figure 3). Among the 4 patients who required NTG in C-IV group, 2 patients underwent laparoscopic appendectomy, 1 patient diagnostic laparoscopy and 1 patient laparoscopic cholecystectomy. Among the 8 patients who required NTG in group N, 5 patients underwent laparoscopic cholecystectomy, 1 patient diagnostic laparoscopy and 2 patients laparoscopic appendectomy.

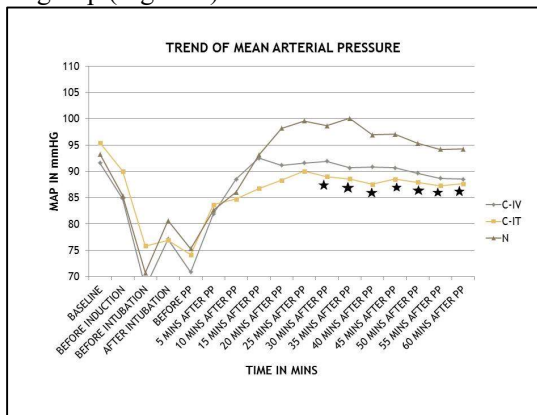


**Figure 3:** Percentage of patients requiring NTG in the different groups

★ Denotes significant difference

between C-IT and C-IV ( $p=0.04$ ),  
 ● Denotes significant difference between C-IT and group N ( $p=0.001$ ).

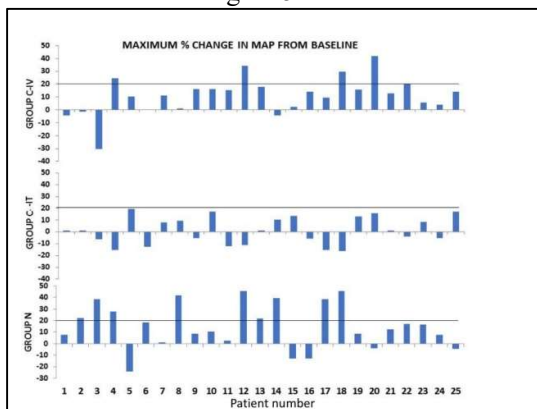
There was a statistically significant difference in the number of patients who required NTG between group C- IT and group C- IV ( $p=0.04$ ) and between the group C- IT and group N ( $p=0.001$ ). The MAP was higher than baseline in group N compared to the other two groups. The MAP was consistently below the baseline (95 vs 90) throughout the period of observation in the IT group (Figure 4).



**Figure 4:** Trend of mean arterial pressure in the three groups. (Values are indicated as mean)

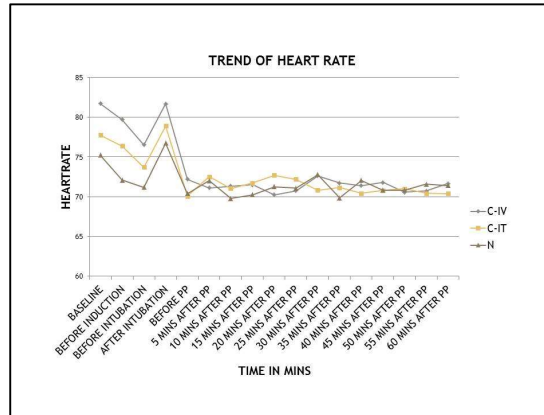
★ Denotes the points where significant difference was noted between C-IT and group N.

The magnitude of maximum change in MAP is shown in Figure 5.



**Figure 5:** Magnitude of change in MAP following pneumoperitoneum as percentage change from baseline. Each bar represents an individual patient. Reference line indicates 20% change above baseline.

HR remained stable in all patients throughout the period of observation (Figure 6).



**Figure 6:** Trend of Heart rate in the three groups. (Values are indicated as mean).

The demand for rescue analgesia was 64% in group C-IV, 40% in group C-IT and 80% in group N in the first two hours. Significantly less number of patients in group C-IT required rescue analgesia than group N.

None of the patients in any group were deeply sedated at extubation. Patients were either ‘Awake and comfortable’ or ‘Asleep and arousable’. Relatively more patients (72%) were awake in group N at extubation. All our patients were awake by 90mins. There is no statistically significant difference in the sedation score between the groups.

Transient hypotension (systolic blood pressure < 80mmHg) was observed in 8 patients (32%) in C-IV group at induction, which responded to 3mg bolus dose of mephenteramine. One patient in C-IV group developed intra-operative bradycardia that was treated with 0.3mg of atropine.

### Discussion

The increase in MAP associated with pneumoperitoneum is the result of both increased IAP and hypercarbia. Abdominal muscle relaxation is an important confounding factor as inadequately relaxed muscles can cause an increase in IAP with consequent effects on haemodynamics.<sup>8</sup> None of the studies so far have monitored the degree of neuro muscular paralysis. We used a TOF monitor as an objective method of maintaining neuro-muscular paralysis. In addition, MAC-age was monitored in all the patients and maintained constantly at 1.0 throughout the procedure and not altered based on haemodynamics. Most other studies

previously done have increased the concentration of agents before starting on NTG. Standardizing the neuromuscular paralysis and the depth of anaesthesia has helped us to interpret the exact pharmacodynamic effects of the two different routes of clonidine.

The number of patients requiring NTG in study done by Tripathi et al was 46% in control group, 6% in the 1µg/kg group and no patients in the 2µg/kg group.<sup>10</sup> Compared to our study less number of patients have required NTG in their study. This is probably because haemodynamics was managed initially by increasing the concentration of sevoflurane to 2% and only when the increase in MAP exceeded 20% from the baseline despite 2% sevoflurane, it was treated with NTG. Omar et al studied the effects of 2µg/kg IV clonidine in laparoscopic surgeries and observed that 6.566% patients required NTG.<sup>11</sup>

The central action of i.v. clonidine on the vasomotor center along with the sequential administration of other anesthetic drugs at induction (propofol, fentanyl) could have resulted in hypotension that was observed in 8 patients in C-IV group. Aho et al in his study described a significant decrease in MAP following induction after giving 4.5µg/kg i.m. clonidine as premedication.<sup>15</sup> In contrast to our observation, no hypotension was reported by Tripathi et al on using 1µg/kg i.v. clonidine.<sup>10</sup> Filos et al compared 150, 300 and 450µg IT clonidine as a sole agent for post op analgesia following caesarean section and observed a decrease in MAP of more than 20% from baseline with 150µg clonidine.<sup>20</sup> We have not observed any hypotension in our study with 1µg/kg IT clonidine. This can probably be due to our patients being subjected to a surgical stress and capnoperitoneum that countered the vasodilating properties of clonidine or due to the smaller dose of clonidine used.

Kumkum et al observed a significant decrease in HR from baseline in patients who were premedicated with 150µg of oral clonidine, but it was not severe enough to demand intervention.<sup>21</sup> Filos et al observed that despite using 450µg of IT clonidine, none of the patients had bradycardia.<sup>20</sup> Similar stability of HR was observed in our study too.

IT clonidine is commonly used as an adjuvant to spinal local anaesthetics to prolong the duration

of analgesia.<sup>17,22</sup> Only Filos et al have used IT clonidine as a sole analgesic for post op analgesia in caesarean section patients and they observed a dose dependent increase in duration of analgesia lasting for 402± 75, 570 ±76 and 864±80mins when 150, 300 and 450 µg were used.<sup>20</sup> They have demonstrated that less clonidine is needed IT than systemically to produce strong analgesic effect lasting for longer duration. The effect of IT clonidine on post-operative analgesia could not be inferred from our study as the duration of analgesia was not assessed. However, we observed that IT clonidine provides good early post op analgesia as the number of patients who required rescue analgesia was less in this group compared to the other two groups. Although less number of patients in C-IT group required rescue analgesia, the difference was not statistically significant.

Tripathi et al have also observed that even with 2µg/kg of i.v. clonidine, none of their patients were deeply sedated.<sup>10</sup>

The limitation of this study is that double blinding could not be done as the route of drug administration involved a technique, i.e. spinal in one group of patients. The other side effects of clonidine such as dry mouth, constipation and postural hypotension was also not followed up. Further, both upper abdominal and lower abdominal procedures were included in our study. So, we could not eliminate the influence of the two positions on haemodynamics. Direction for future research should be towards determining the risk vs benefit analysis of intrathecal vs intravenous clonidine.

### Conclusion

In patients undergoing laparoscopy under GA, 1µg/kg spinal clonidine produces better haemodynamics during insufflation and maintenance of capnoperitoneum than an equal dose of i.v. clonidine. Clonidine administration by both i.v. and i.t. route provides good early post op analgesia. At 1µg/kg neither i.v. nor i.t. clonidine causes deep sedation delaying extubation or discharge from post-anaesthesia care unit.

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