The Effect of Clonidine on Hemodynamics, Recovery and Post-Operative Pain in Laparoscopic Gynaecological Surgeries: A Comparative Study Involving Two Routes of Administration

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ABSTRACT

Background: *Laparoscopy requires creation of a pneumoperitoneum which produces a significant rise in heart rate, mean arterial pressure, reduction in venous return and systemic vascular resistance. Various pharmacologic agents are used to control hemodynamic changes associated with pneumoperitoneum.*

Aim: *To compare the effects of Clonidine administered intravenously (group IV) and intraperitoneally (group IP) on hemodynamics,recovery and post-operative pain in patients undergoing elective laparoscopic gynaecological surgeries.*

Study design: *Randomized controlled trial.*

Methodology: *Sixty patients undergoing elective laparoscopic gynaecological surgeries were selected. General anaesthesia was administrered in all cases.After inserting ports Group IV: received Clonidine 1µg/kg i.v along with Ropivacaine 0.25% 20cc intraperitoneally using a ryles tube introduced and directed towards hepatophrenic recess Group IP: received Clonidine 1µg/kg along with Ropivacaine 0.25% 20cc.intraperitoneally Vitals weremonitored every 30min during the procedure. Postoperatively oxygen saturation, heart rate, and blood pressure weremonitored.Aldrete recovery scoring system was used to assessreadiness for discharge. When the score was>8, and pain was monitored using VAS scoring in lying and sitting posture next 12hours.*

Statistical Analysis: *Continous data was analysed using student t-test while categorical data was analysed using fisher's exact test and chi square test.*

Results:*Intravenous Clonidine significantly reduced the MAP (group IP: 80.5±6.7,group IV: 67.44±5.6) during intraoperative period while intraperitoneal group showed reduced MAP in postoperative period (group IP: 75.98±7.35, group IV: 83.36±17.05). Heart rate both during intraoperativeperiod (group IP: 63.2±6.35, group IV: 77.6±9.35) and postoperative period (group IP: 75.6±7.35, group IV: 83.36±17.05) showed significant decrease in intraperitoeal group. Intraperitoneal Clonidine showed better hemodynamic control by maintaining heart rate and MAP postoperatively and better recovery profile in the form of VAS Scoring(2.0±0.618 p value <0.05) and time to request first rescue analgesia(6.567±0.9 p value <0.05).*

Conclusion: *Clonidine when added to ropivacaine (0.25%) intraperitoneally provide better hemodynamic control and prolonged analgesia with less side effects than intravenous clonidine.*

Keywords: *Clonidine, Ropivacaine, Intravenous, Intraperitoneal, laparoscopic surgery*

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INTRODUCTION

Laparoscopy has been promoted aggressively as "gentle" surgery with minimal tissue trauma, reduced postoperative complications, and early recovery to normal level of activity. This indeed is generally true, but the procedure is not risk free. Laparoscopy requires creation of a pneumoperitoneum to help the surgeon visualize the area of interest. Pneumoperitoneum is a complex but well-tolerated pathophysiologic state with significant haemodynamic effects.[2] Pneumoperitoneum with an intraabdominalpressure of >14 mmhg produces a significant rise in heart rate, mean arterial pressure, reduction in venous return and systemic vascular resistance. Although systemic vascular resistance falls, cardiac output is maintained by increase in heart rate. These changes produce considerable effects in patients with cardiac disease who may not be able to cope up with increased myocardial oxygen requirements and decreased cardiac output. Recent studies concerning laparoscopic cholecystectomy have, however indicated that the stress responses measured by intraoprative serum levels of cortisol and catecholamine, is not diminished by the laparoscopic approach,but may be even be increased in comparison with open techniques.[3]

Various pharmacologic agents like Propofol, Esmolol, Lignocaine, α_2 adrenergic receptor agonists like Clonidine are used to control hemodynamic changes associated with pneumoperitoneum. Alpha-2 adrenergic receptor agonists has been prescribed historically as an antihypertensive agent. It has found to be used in treatment of neuropathic pain, opioid detoxification, sleep hyperhidrosis, attention-deficit hyperactivity disorder (ADHD) etc. α_2 adrenergic

receptor agonists reduce the requirements of both intravenous and inhalational anaesthetic agents, produce sedation and anxiolysis with good analgesic properties.[5]

Clonidine is a centrally-acting α-adrenergic receptor agonist with more affinity for α_2 than α_1 receptors. It selectively stimulates receptors in the brain that monitor catecholamine levels in the blood. These receptors close a negative feedback loop that begins with descending sympathetic nerves from the brain that control the production of catecholamines in the adrenal medulla. By fooling the brain into believing that catecholamine levels are higher than they really are, Clonidine causes the brain to reduce its signals to the adrenal medulla, which in turn lowers catecholamine production and blood levels, thus modulating hemodynamic changes induced by pneumoperitoneum.[4] Clonidine is available as tablets ,transdermal patch andinjectable forms for neuroaxial (epidural & sub arachnoid) use.

Neuroaxially administered Clonidine produces analgesia, partially mediated by α_2-adrenoceptor-induced, synthesis of nitric oxide (NO) and by stimulation of cholinergic interneurons in the spinal cord.The central mechanisms by which Clonidine produces its antinociceptive effects are still speculative. Although Clonidine may produce adverse effects like dry mouth, sedation, hypotension and bradycardia, it does not produce respiratory depression.

Recent studies show that Clonidine has specific effects on peripheral nerves by neuro modulation. When given intraperitoneally, Clonidine has produced more effective analgesia in combination with local anaesthestic agent by acting on local nerves.[6]Ropivacaine is a local anaesthetic drug belonging to the aminoamide group. The name Ropivacaine refers to both the racemate and the marketed S-enantiomer. Ropivacaine was developed after bupivacaine was noted to be associated with cardiac arrest, particularly in pregnant women. Ropivacaine is indicated for local anaesthesia including infiltration, nerve block, epidural and intrathecal anaesthesia in adults and children over 12 years. It is also sometimes used for infiltration anaesthesia for surgical pain in children.Recent studies had shown that intraperitonealnebulisation during laparoscopy also have good analgesic effect.[9,10]

We intend to compare the effects of Clonidine administered intravenously and intraperitoneally in maintaining homodynamic stability during the surgical (laparoscopic) procedure. Patient's postoperative recovery scores and pain relief were compared to find whether intraperitoneal Clonidine has any added advantages over intra venous route

AIM AND OBJECTIVE

To compare the effects of Clonidine administered intravenously (group IV) and intraperitoneally (group IP) along with intraperitoneal Roivacaineon hemodynamics, recovery and post-operative pain in patients undergoing elective laparoscopic gynaecological surgeries.

METHODOLOGY

Sixtypatients were selected randomly according to computer generated random numbers based on exclusion and inclusion criteria.

Inclusion criteria:

American society of anesthesiologists grading (ASA) I & II
15-65yrs of age
Laparoscopic gynaecological surgery.
Duration of surgery 1-2hrs

Exclusion criteria:

ASA III & IV
Uncontrolled hypertension
Bradycardia pulse rate<60/min
Heart disease
Patient not willing for study
Laparoscopic gynaecologicalsurgery converted to open technique
Emergency surgery
Patients were divided into two equal groups.
group (IV) Clonidine 1µg/kg intravenously and Ropivacaine 20cc of 0.25% intraperitoneally
group (IP) Ropivacaine 20cc of 0.25% +Clonidine 1µg/kg intraperitoneally

PROCEDURE:

All the cases were done under general anaesthesia. Patients were premedicated with inj. Glycopyrolate 10µg/kg, inj, Midazolam 0.05mg/kg and inj. Fentanyl 2µg/kg i.v before induction. Group IV patients will receive Clonidine 1µg/kg i.v before intubation inj. Propofol 2mg/kg and inj. Vecuronium 0.1mg/kg used to facilitate tracheal intubation. inj. Ondansetron 0.15mg/kg given at the end of surgery.

Group IV patients received Clonidine 1µg/kg i.v before intubation. Once the second port is inserted under direct vision ryles tube introduced and directed towards hepatophrenic recess and injection Ropivacaine 0.25% 20cc given in group i.v. In group i.p patients received inj. Ropivacaine 0.25% 20ccalong with Clonidine 1µg/kg intraperitoneally.

Peripheral oxygen saturation, heart rate, blood pressure were monitored every 30min during the procedure.Patients were also noted for time when inhalational agents shut off(ti), time to open eyes open on commands(to), time to extubated(te) alderete recovery scoring(ta) when the score is >8, pain monitored using VAS scoring in lying and sitting posture,time to request of rescue analgesic(rescue) and time to return of bowel movements(bm)

Postoperatively heart rate, blood pressure, temperature, were monitored. Aldrete recovery scoring monitored, when the score is >8, pain monitored using VAS scoring in lying and sitting posture. All monitoring was donefor first 30min and then hourly for 12hrs.injection Tramadol 50-100mg was given as rescue analgesia.Mean and standard deviation were calculated using MS Excel worksheet(descriptive statistics). Further statistical analysis was performed using SPSS software. The statistical tests used in this study were student t test(to compare two mean and standard deviation) and chi square test. For all statistical analysis p <0.05 was considered statistically significant.

OBSERVATION AND RESULTS

Statistical analysis of the data showed there was no significant difference in demography and saturation. Our study showed intravenous Clonidine significantly reduced the MAP (group IP: 80.5±6.7, group IV:67.44±5.6)during intraoperative period while intraperitoneal group showed reduced MAP in postoperative period (group IP:75.98±7.35, group IV:83.36±17.05). Heart rate both during intraoperative period(group IP:63.2±6.35, group IV:77.6±9.35) and postoperative period (group IP:75.6±7.35 ,group IV: 83.36±17.05)showed significant decrease in intraperitoeal group than intravenous group. Intraperitoneal Clonidine showed better hemodynamic control by maintaining heart rate and MAP postoperatively and better recovery profile in the form of VAS Scoring(2.0±0.618 p value <0.05) and time to request first rescue analgesia(6.567±0.9 p value <0.05).

Demography

ASA (chi square test)

	IV	IP	P VALUE
I	22	20	0.7787
II	8	10	

	IV	IP
Mean	41.4	42.5
Standard deviation	3.4	3.47
P value	0.2199	

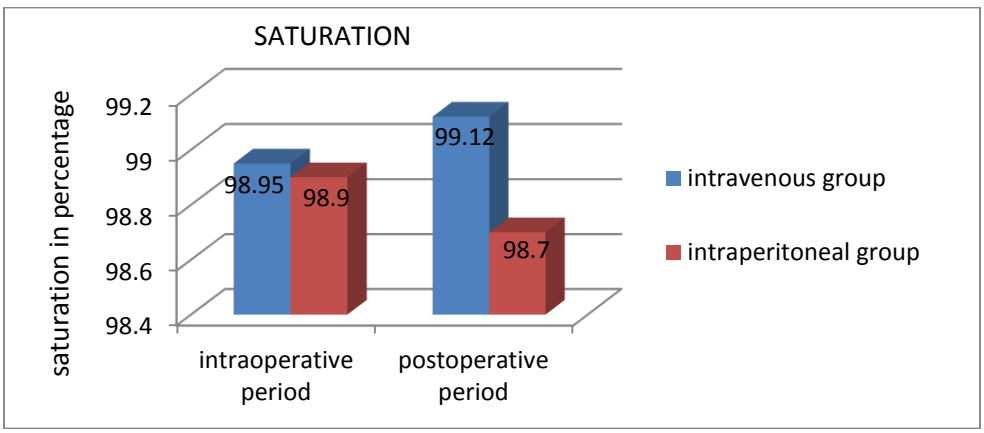
AGE (in years) (student t test)

	IV	IP
Mean	49.64	50.55
Standard deviation	2.475	3.474
P value	0.2474	

WEIGHT (Student t test)

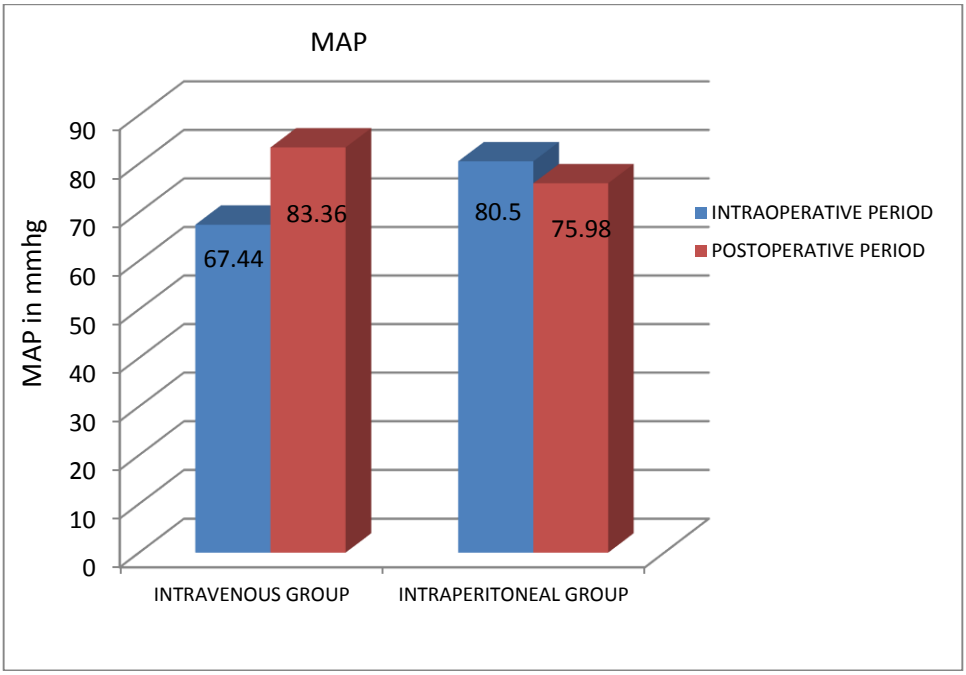
Saturation (%) (Student t test)

Monitoring	Route	Intraoperative (mean ±SD)	Postoperative (mean±SD)
Saturation (%)	i.v	98.95±0.87	99.12±1.3
	i.p	98.9±0.13	98.7±1.17
	P value	0.7576	0.1936



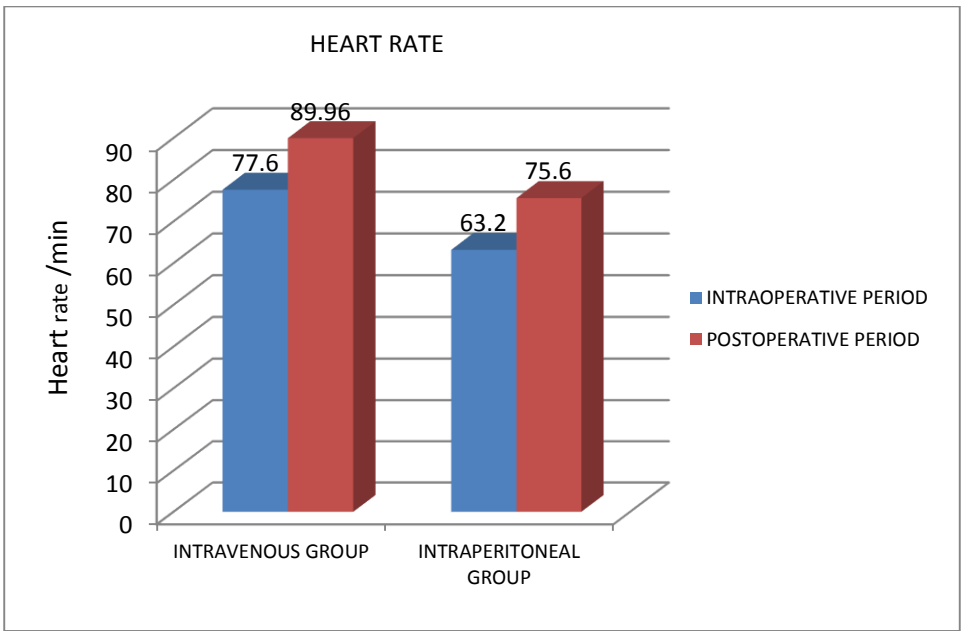
MAP (mmhg) (student t test)

Monitoring	Route	Intraoperative	Postoperative
MAP(mmhg)	i.v	67.44±5.6	83.36±17.05
	i.p	80.5±6.7	75.98±7.35
	P value	0.0001	0.0336



Heart rate/min(student t test)

Monitoring	Route	Intraoperative	Postoperative
Heart rate/min	i.v	77.6 ±9.19	89.96±6.04
	i.p	63.2±6.35	75.6±7.77
	P value	0.0001	0.0001



group	Ti(hrs)	To(min)	Te(min)	Rescue(hrs)	Bm(hrs)	Total Dose of tramadol mg
i.v	1.46±0.869	4.5 ±0.98	5.5±0.976	3.04±0.968	11.89±0.9	85±15
i.p	1.51±0.786	4.4±0.897	5.67±0.876	6.567±0.9	9.98±0.768	50±17.05
P value	0.8160	0.6817	0.4806	0.0001	0.0001	0.0001

VAS scoring (student t test)

Monitoring	Route	Postoperative
VAS (lying)	i.v	2.8±0.798
	i.p	2.0±0.618
	P value	0.0001
VAS (sitting)	i.v	2.7±0.98
	i.p	2.0±0.7
	P value	0.0023

Complications (Chi Square Test)

	No. of Cases	Group IV	Group IP	p value
Hypotension	60	9	1	0.0122
Bradycardia	60	7	3	0.2990
Nausea	60	3	3	1.0000
Vomiting	60	7	3	0.2990
Shivering	60	3	8	0.0575
Dry mouth	60	3	3	1.0000
Shoulder pain	60	16	5	0.0061

DISCUSSION

Post-operative pain after laparoscopic surgeries consists visceral and parietal components. Previous studies[9,10] suggest that predominant cause of pain is parietal but in contrast many other studies emphasized that in early convalescent period, major portion is occupied by visceral pain because as compared to small incisions and limited trauma to the abdominal wall, the surgical manipulation and tissue destruction in visceral organs is much more.[17,18]

In laparoscopic surgeries gas insufflations causes raisein intraperitoneal pressure leading to peritoneal inflammation and neuronal rupture. There is linear relationship between abdominal compliance and severity of post-operative pain. We choose intraperitoneal route because it blocks the visceral afferent signals and modifies visceral nociception. The local anaesthetic agents provide antinociception by affecting nerve membrane associated proteins and by inhibiting the release and action of prostaglandins which stimulates the nociceptors and cause inflammation. Intraperitoneal instillation of 0.25% bupivacaine provided effective analgesia when combines with Dexmedetomidine or Tramadol.(19) Hence in this study we compared the effect of intraperitoneal Clonidine with Ropivacine 0.25% and combination with intravenous Clonidine with Ropivacine 0.25% intraperitonealfor laparoscopic gynaecological surgeries.

Memis et al(6) studied effect of combining Tramadol and Clonidine on intraperitoneal bupivacaine 0.25%and showed that addition of Tramadol or Clonidine decreased VAS scoring(p value<0.5)when compared with plain Bupivacine, the time for requesting rescue analgesia(groupB:30min,group BT:120min, BC:110min) and total analgesic dose(Group B:76.7±10.1, group BT:63.9±8.4, Group BC:70±5.2).

Shukla et al(19) showed the same results by combining Tramadol or Dexmedetomidine to intraperitoneal Bupivacine. Time to request rescue analgesia (Group B:55±18, group BT:118±22, Group BD:128±20 min)and total dose of rescue analgesia required also significantly low in Dexmeditomidine group (Group B:175±75, group BT:85±35, Group BD:45±35 mg).

Our study correlate with the above studies.The two groups were comparable with respect to their age, weight, sex and ASA Physical status. There was no statistically significant difference among two groups in demographic profile. Both groups were comparable with respect to time to shut off inhalational agents,time to open eyes and time to reach alderete scoring of >8

There was significant decrease in VASin lying down posture (group IP:2.0±0.618,group IV:2.8±0.798) and VAS in sitting (group IP:2.0±0.7, group IV:2.7±0.98). there was significant difference in time to request recue analgesia(group IP:6.567±0.9, group IV:3.04±0.968 hrs). our study showed the similar result as memis et al(6), shukla et al(19) in dose of rescue analgesia required(group IP:85±15,group IV:50±17.05 mg)

In study done by memis et al(6) the groups were comparable in respect to SpO2 similar to our

study. However, they showed significant decrease in heart rate and MAP in Tramadol and Clonidine group.In contrast our study showed intravenous Clonidine significantly reduced the MAP(group IP:80.5±6.7,group IV:67.44±5.6)during intraoperative period while intraperitoneal group showed reduced MAP inpostoperative period (group IP:75.98±7.35, group IV:83.36±17.05). Heart rate both during intraoperative period (group IP:63.2±6.35, group IV:77.6±9.35) and postoperative period (group IP:75.6±7.35, group IV:83.36±17.05) showed significant decrease in intraperitoeal group than intravenous group. Our study also showed that there was early return of bowel movements in intraperitoneal Clonidine group when compared to intravenous Clonidine group (group IP:9.98±0.768, group IV:11.89±0.9 hrs).

Intraperitoneal Clonidine group had lesshypotention (p value<0.05), less vomiting and significantly less shoulder pain (group iv-16 & group ip-5; p value =0.0061) compared to the intravenous Clonidine group. While intravenous Clonidine showed more control on shivering than intraperitoneal Clonidine. Above results correlate with study done by shukla et al.[19]

CONCLUSION

We conclude that intraperitoneal instillation of Clonidine 1 μ/kg in combination with Ropivacaine 0.25% in elective laparoscopic gyneacological surgeries significantly reduces the post-operative pain and reduces the analgesic requirement in post-operative period as compared to intravenous Clonidine and can be used as an alternative route for laparoscopic surgeries.

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