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COMPARISION OF ORAL PREGABALIN VERSUS BOLUS DOSE OF INTRAVENOUS DEXMEDETOMIDINE IN ATTENUATING THE HEMODYNAMIC RESPONSES DURING LARYNGOSCOPY, INTUBATION AND PNEUMOPERITONIZATION IN LAPROSCOPIC CHOLECYSTECTOMY: A RANDOMIZED STUDY

Anaesthesiology

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ABSTRACT

Background: Laryngoscopy, intubation and pneumoperitoneum during general anaesthesia are severe noxious stimuli that can produce many adverse effects. Aim of the study was to compare the efficacy of oral pregabalin versus intravenous bolus dose of dexmedetomidine as premedication for attenuating the haemodynamic pressor response during intubation, pneumoperitonization and extubation as well as perioperative stability and requirement of postoperative analgesics. **Methods:** A Randomised study was conducted in 100 patients undergoing Laparoscopic Cholecystectomy. Participants were divided into two groups in which group P (n=50) received oral pregabalin 150mg with sips of water 1 hour prior to surgery and intravenous normal saline (0.9%) 10ml, 10 mins prior to induction over 10 minutes and those in group D (n=50) received oral placebo tablet with sips of water 1 hour prior to surgery and intravenous dexmedetomidine at 1mcg/kg diluted with normal saline (total volume 10ml), 10 minutes prior to induction over 10 minutes. Hemodynamic parameters like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SPO2) and ETCO2 were noted before premedication and induction (baseline), at the end of induction and at laryngoscopy and intubation (I0) and then at 1,3,5,10 minutes after intubation as well as at start of pneumoperitoneum and then after every 10 minutes interval till the deflation of CO2 and also at the time of extubation and 10 minutes thereafter. Postoperative pain assessment done by VAS score at various time intervals and Postoperative sedation by Ramsay Sedation Scale (RSS).

KEYWORDS

Postoperative pain, Postoperative sedation, VAS score, Ramsay Sedation Scale (RSS)

INTRODUCTION:

Laparoscopic abdominal surgery is one of the most commonly performed surgery in present era as it has many advantages over open surgery like less postoperative pain, shorter hospital stays, early mobilization, faster recovery and better cosmetic results[1]. Laryngoscopy, intubation and pneumoperitoneum during general anaesthesia are severe noxious stimuli that can produce an intense sympathetic stimulation leading to increased level of serum catecholamines and vasopressin which further leads to adverse hemodynamic response like tachycardia, hypertension, arrythmias etc[2].

In addition, increased intrabdominal pressure with raised diaphragm as well as reverse trendelenburg position required for surgery may result in adverse cardiopulmonary changes like diminished venous return, decreased cardiac output, elevated arterial pressure and increased systemic and pulmonary vascular resistance. These adverse hemodynamic changes may predispose to myocardial ischemia which may be life threatening in vulnerable patients[2,3].

Various studies[4,5,6] have been done to attenuate these sympathoadrenal response to pneumoperitoneum and intubation which include deepening the plane of anaesthesia with inhalational or intravenous anaesthetic agents, decreasing the duration of laryngoscopy to less than 15 seconds. Various drugs like lidocaine, sedatives, sodium nitroprusside, calcium channel blockers, beta blockers, alpha-2 agonists (clonidine, dexmedetomidine), magnesium sulphate and GABA analogues like gabapentin, pregabalin etc have also been used but the drug of choice is still not proven.

Pregabalin acts on calcium channels and reduces or modulates the release of several excitatory neurotransmitters including glutamate, norepinephrine, substance p and calcitonin gene related peptide producing inhibitory modulation of "overexcited" neurons and returning them to "normal" state[7]. Several studies[4,5,6,8] have been done to evaluate the efficacy of pregabalin as a post-operative analgesic but only few studies are available in literature for attenuation of pressor response during airway instrumentation and pneumoperitonization.

Dexmedetomidine has properties of analgesia, sympatholysis and titrating sedation without major respiratory depression. Intravenous use of dexmedetomidine has been found to decrease the serum catecholamine levels to blunt the hemodynamic response to pneumoperitoneum, laryngoscopy, intubation and extubation.

This study aims to evaluate and compare the efficacy of oral pregabalin versus intravenous bolus dose of dexmedetomidine as premedication for attenuating the haemodynamic pressor response during intubation, pneumoperitonization and extubation as well as perioperative stability and requirement of postoperative analgesics.

RESULTS:

Table 1: Comparison of heart rate (HR) changes during intubation and laryngoscopy between two groups

Time	Heart rate (Mean ± SD)		P value
	GroupD(n=50)	Group P(n=50)	
Baseline (before premedication)	84.82±12.32	85.92±18.04	0.72
Baseline (before induction)	84.49±13.62	88.1±16.63	0.24
At the end of induction	81.06±14.37	90.22±17.21	0.01
At laryngoscopy and intubation I_0	84.94±15.11	93.59±17.47	0.01
I_1	81.61±14.32	89.92±14.48	0.01
I_3	78.29±13.84	88.73±16.3	<0.001
I_5	79.67±17.85	87.78±16.66	0.02
I_{10}	84.2±19.49	89.29±16.08	0.16

For Heart rate a significant decrease in the mean heart rate was observed in group D at 3 and 5 minutes after intubation when compared to baseline ($p<0.05$) while in group P, there was significant increase in the mean HR from baseline at the time of laryngoscopy and intubation. Decrease in HR was more in group D when compared to group P from the end of induction till 5minutes after intubation, which was found to be statistically significant ($p<0.05$).

For SBP there was significant decrease in mean SBP from baseline in group D at 1, 3, 5 and 10minute after intubation. In group P there was

Table 2: Comparison of changes in systolic blood pressure (SBP mmHg), diastolic blood pressure (DBP mmHg) and mean arterial pressure (MAP mmHg) during intubation and laryngoscopy between two groups

Time	SBP (Mean ± SD)		P value	DBP (Mean ± SD)		P value	MAP (Mean ± SD)		P value
	Group D	Group P		Group D	Group P		Group D	Group P	
Baseline (before premedication)	133.49±16.29	130.29±19.17	0.37	84.29±10.25	85.82±11.04	0.48	101.73±15.22	101.52±14.16	0.94
Baseline (before induction)	138.71±22.37	135.35±16.89	0.4	89.27±12.9	87.71±9.93	0.51	106.54±17.41	103.96±13.05	0.41
At the end of induction	126.49±26.52	123.14±19.63	0.48	82.55±16.42	82.49±12	0.98	99.44±21.37	96±14.09	0.35
At laryngoscopy and intubation I_0	125.92±20.84	130.02±26.77	0.4	84.98±15.01	84.27±18.29	0.83	98.67±19.52	106.72±17.8	0.03
I_1	119.37±22.41	121.45±23.59	0.66	80.06±17.86	81.82±15.82	0.61	92.94±16.5	100.06±16.18	0.03
I_3	111.63±14.85	117.33±17.47	0.09	75.06±16.57	76.85±13.42	0.56	87.29±16.67	95±14.8	0.02
I_5	117.2±17.51	117.9±17.5	0.84	81.35±13.29	82.18±15.59	0.78	91.98±16.43	99.32±10.77	0.01
I_{10}	117.43±14.21	121.82±16.08	0.16	83.22±13.07	84.73±13.78	0.58	94.1±14.96	103.94±12.01	<0.001

significant decrease in mean SBP from baseline at 3 and 5 minutes after intubation. The decrease in mean SBP was more in group D as compared to group P from laryngoscopy and intubation till 10minutes after intubation, which was found to be statistically significant (p<0.05).

For DBP a significant fall in mean DBP from baseline was observed in both the groups at the end of induction and at 3 minutes after intubation (p<0.05). Decrease in mean DBP was more in group D as compared to group P which was found to be statistically significant from 1minute after intubation till 10 minutes (p<0.05).

For MAP a significant fall in mean MAP from baseline was observed in group D at 1,3,5,10-minute interval compared to baseline while it remained stable at all other time intervals (p<0.05). In group P a significant rise in the mean MAP from baseline was observed at laryngoscopy and intubation, however it remained stable at all other time intervals. Decrease in MAP was more in group D from I0 to I10 which was found to be statistically significant.

For Heart rate no significant change was observed baseline at various time intervals following pneumoperitonization in both the groups however, decrease in HR was significantly more in group D than in group P as compared to group P at all time points. A significant increase in HR from baseline was observed at the time of extubation in both the groups (P<0.05).

Table 3: Comparison of heart rate and MAP changes from start of pneumoperitoneum till 10minutes after extubation between two groups

Time	Heart rate (Mean ±SD)		P value	MAP (Mean ±SD)		P value
	Group D	Group P		Group D	Group P	
At the start of pneumoperitoneum P0	80.76±15.7	89.12±16.29	0.01	88.76±17.33	95.56±16.19	0.05
P 15	86.24±16.11	91.71±14.56	0.08	93.73±16.82	101.46±12.84	0.01
P 25	83.02±14.59	91.41±16.68	0.01	95.78±15.13	110.42±14.91	<0.001
P 35	84.14±14.67	94.45±13.27	<0.001	94.1±15.74	102.06±13.17	0.01
P 45	83.02±13.74	91.17±13.78	<0.001	91.02±9.19	99.18±18.88	<0.001
P 55	84.15±14.15	87.93±13.33	0.2	92.2±9.89	96.15±13.43	0.11
Deflation of CO_2	80.51±12.39	90.18±16.54	<0.001	89.86±10.58	97.76±15.19	<0.001
At the time of extubation	92.33±17.27	98.02±18.27	0.12	111.51±19.73	120.74±15.14	0.01
10 minutes after extubation	83.37±14.43	98.33±25.07	<0.001	93.88±14.43	99.5±14.56	0.06

For MAP increase in MAP during 30minutes of pneumoperitoneum was more in group P from baseline which was found to be highly significant (p<0.05) however in group D there was no significant rise in MAP from baseline. At the time of extubation both groups showed a significant rise in MAP from baseline.

Table 4: Comparison of changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from start of pneumoperitoneum till 10 minutes after extubation between two groups

Time	SBP (Mean ± SD)		P value	DBP (Mean ±SD)		P value
	Group D	Group P		Group D	Group P	
At the start of pneumoperitoneum P0	113.47±16.29	120.94±19.34	0.04	77.33±14.44	80.86±13.12	0.21
P 15	119.67±15.56	126.76±13.24	0.02	85.12±14.73	91.76±8.96	0.01
P 25	120.86±14.59	130.49±18.5	0.01	85.94±12.18	93.57±12.98	<0.001
P 35	119.35±15.17	127.79±18.04	0.02	82.41±14.01	89.84±13.02	0.01
P 45	115.49±11.77	126.79±14.2	<0.001	80.18±9.67	85.47±13.04	0.02
P 55	116.89±11.77	121.59±11.57	0.06	80.54±9.78	85.71±9.69	0.01
Deflation of CO_2	116.27±13.29	130.33±25.32	<0.001	78.8±8.79	81.96±12.01	0.14
At the time of extubation	141±22	151.18±22.47	0.03	95.88±14.33	103.98±14.43	0.01
10 minutes after extubation	122.78±17.48	126.63±15.15	0.25	81.16±11.11	87.38±12.55	0.01

For SBP a significant rise in mean SBP from baseline was observed in both groups at the time of extubation and 10minutes after extubation. However, the mean SBP remained stable at all other time interval. The decrease in mean SBP was significantly more in group D when compared to group P (p<0.05).

For DBP a significant rise in mean DBP from baseline was observed in group D and group P following CO2 insufflation (P10) and at P20 in both the groups but this rise was highly significant in group D as compared to
group P (p<0.05).

DISCUSSION:

Laparoscopic cholecystectomy is considered gold standard and one of the most commonly practiced surgeries for gall bladder diseases under general anaesthesia in the present era due to its well-known advantages. This study was designed to compare oral pregabalin versus bolus dose of intravenous dexmedetomidine as premedication in attenuating the hemodynamic responses to laryngoscopy, intubation and also during pneumoperitoneum in laparoscopic cholecystectomy.

(1) Effect on Heart rate:

[Table no.1] In our study group D showed decrease in mean HR from baseline (84.82±12.32) following laryngoscopy and intubation and maximum decrease was at 3min (78.29±13.84) and 5min (79.67±17.85) intervals which was highly significant (p<0.001) while a significant increase in HR (p<0.05) from baseline (85.92±18.04) was observed in group P following laryngoscopy and intubation which was maximum at I0 (93.59±17.47) and it never reached to baseline at all time intervals after intubation till 10min after extubation.

[Table no.3] No significant change was observed in HR values from the values at start of pneumoperitoneum till deflation though at the time of extubation both groups showed a significant increase in HR from baseline ($p<0.05$). When comparing two groups, HR remained near to baseline in group D as compared to group P at all time intervals which was found to be statistically significant ($p<0.05$).

Similarly, a significant reduction in HR following loading dose of dexmedetomidine after intubation, after 20minutes of pneumoperitoneum as compared to saline group was observed in a study done by Vora K.S et al [2015][9]

Rastogi B et al [2012][10] studied the effect of two different doses of oral pregabalin (75mg and 150mg) as premedication for attenuation of pressor response and observed an increase in HR in group P150 from baseline (85.92±18.04) after 1min of laryngoscopy (89.92±14.48) which was similar to our study however Gupta K et al [2011][11] reported that after premedication with oral pregabalin (150mg) and placebo, there was a significant increase in HR in both groups but the increase was less in pregabalin group (89.29±16.08) than placebo group.

(2) Effect on Blood Pressure

[Table no.2] In our study we observed the intraoperative systolic blood pressure (SBP) during laryngoscopy and intubation was found to be statistically significant among both the groups ($p<0.05$). There was significant decrease in mean SBP (mmHg) from baseline (133.49±16.29) in group D at laryngoscopy and intubation IO (125.92±20.84) while in group P mean SBP increased (130.29±19.17) from baseline (130.02±26.77) at Io which was found to be statistically significant ($p=0.03$). After Io from I1 to I10, both the groups showed decrease in mean SBP but this decrease was more in group D as compared to group P ($p<0.05$).

[Table no.3 and 4] During pneumoperitoneum there was increase in mean SBP from baseline which was observed in both groups though it was not statistically significant but when compared two groups increase was more in group P than group D which was found to be statistically significant ($p<0.05$). A significant fall in mean DBP from baseline was observed in both the groups at the end of induction and at 3minute after intubation ($p<0.05$). Mean DBP was significantly low in group D when compared to group P till 10minutes after intubation ($p<0.05$). An increase in mean DBP from baseline was observed in group D and group P following CO_2 insufflation from 10minutes to 30minutes duration and this increase was more in group P when compared to group D($p<0.05$).

We recorded a significant decrease in MAP (98.67±19.52) from baseline (101.73±15.22) in group D at the time of laryngoscopy and intubation, and maximum decrease was found at 3min after intubation (87.29±16.67) while in group P there was a significant increase in MAP (106.72±17.8) from baseline (101.52±14.16), though following intubation there was no significant change from baseline. When comparing both the groups, fall in MAP was significantly more in group D than in group P ($p<0.05$).

Sebastian B et al [2017][12] observed a statistically significant higher values of HR, SBP, DBP and MAP at all time intervals post intubation in group A (control group) when compared to group B (Dexmedetomidine 0.5μg/kg) and group C (Dexmedetomidine 0.75μg/kg). In group C the MAP decreased from baseline (93.27±5.53) at 3min after intubation (90.27±5.49) which was found to be statistically significant ($p<0.05$).

Rastogi B et al [2012][10] observed a decrease in MAP from baseline after induction in patients receiving two different doses of pregabalin (75mg, 150mg) but this attenuation was significant in group PG150 (87.06±3.90) when compared to baseline (93.15±2.59) ($p<0.05$).

Meena R et al [2016][13] also reported significant increase in MAP from baseline (91.14±4.16) in patients receiving oral diazepam (106.44±6.24) than those receiving pregabalin only.

In present study there was an increase in mean values of SBP, DBP and MAP from baseline in both the groups during pneumoperitoneum though it was statistically insignificant($p>0.05$) but this increase was more in pregabalin group when compared to dexmedetomidine group which was found to be statistically significant($p<0.001$).

We observed an increase in MAP by 7.02mmHg and 5.34mmHg in group D from while it was 14.86 mmHg and 6.5mmHg in group P from at 25minutes and 35minutes time interval from baseline respectively, and this difference was found to be statistically significant between two groups ($p<0.05$).

Following deflation of CO_2, the mean value of MAP decreased to baseline value (P_0) in both the groups, but at the time of extubation there was an increase in MAP by 22.75mmHg in group D as compared to 25.18 mmHg in group P which was found to be statistically significant in between two groups ($p<0.05$). This difference shows that in attenuating the stress response during pneumoperitonization, dexmedetomidine is better than pregabalin.

Vora KS et al [2015][9] also observed a significant decrease in MAP in patients who received dexmedetomidine infusion at various time intervals following laryngoscopy and intubation till deflation of CO_2 than in patients who received saline infusion ($p<0.05$).

Manne GR et al [2014][14] reported significant decrease in MAP after starting the infusion (dexmedetomidine 1μg/kg) and there was no significant rise in MAP during pneumoperitonization till release of CO_2 ($p<0.001$)

(3) Post-operative pain

In our study, group P patients experienced more postoperative pain with higher VAS score at various time intervals (from 30 minutes to 24 hours postoperatively) as compared to group D ($p<0.05$).

Pathak AS et al [2016][15] compared the two different doses of dexmedetomidine (1mcg/kg and 0.7mcg/kg) given preoperatively as bolus in patients undergoing laparoscopic surgery and found better postoperative analgesia with lower VAS scores and delayed time duration for first rescue analgesia in patients receiving dexmedetomidine 1μg/kg.

Esmat IM et al [2015][16] showed there was significant reduction in VAS Score in patients receiving two different doses of pregabalin (150mg, 300mg) 1 hour prior to surgery. Pain scores was lower in pregabalin 300mg compared to those receiving pregabalin 150mg.

(4) Sedation score

In our study the sedation score obtained were higher in group D than group P at all time intervals ($p<0.05$) but no patients in both the groups had sedation score more than ≥4. Dexmedetomidine in a dose of 1mcg/kg has been shown to cause increased sedation levels Sebastian B et al [2017][12] found that there were higher sedation scores in dexmedetomidine groups (dex 0.5, 0.75μg/kg) than normal saline ($p<0.05$).

Similarly, Manne GR et al [2014][14] also observed increasing sedation levels in patients receiving low dose dexmedetomidine infusion (0.2μg/kg/h, 0.4μg/kg/h). Various studies with different doses of pregabalin (75mg, 150mg, 300mg) evaluated the effects on anxiolysis and sedation and found that sedation scores were higher with increasing dose of pregabalin.

CONCLUSIONS:

To conclude both dexmedetomidine (1μg/kg IV bolus) as well as pregabalin (150 mg orally) given as premedication for laparoscopic cholecystectomy, maintained the hemodynamic stability during laryngoscopy, intubation and pneumoperitonization but dexmedetomidine was found to be significantly superior in ameliorating the haemodynamic responses to laryngoscopy and laparoscopy along with better postoperative analgesia without any significant adverse effects.

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