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Effect of Adding Intrathecal Dexmedetomidine Neostigmine and Clonidine as an Adjuvant to Hyperbaric Bupivacaine for Elective Cesarean Section

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Abstract:

The delivery of the infant into the hands of a conscious and pain free mother is one of the utmost exciting and satisfying moments in medicine Opioids, although useful as adjuvants, are linked with detrimental side effects. Hereafter crucial adjuvants that can be used with bupivacaine for stable intraoperative circumstances and extending the postoperative analgesia with minimized side effects are being the objective from long back. The p r es ent study was aimed to evaluate and compare the scope of d es i r a b le analgesic efficacy by injecting bupivacaine alone and in combination with dexmedetomidine, clonidine, and neostigmine intrathecally in elective lower abdominal cesarean section, over the early postoperative hours, in a randomized, double-blind comparative study.

Materials and Methods:

A comparative study of intrathecal bupivacaine alone and combined regimen of dexmedetomidine, clonidine, and neostigmine on 120 Patients were randomized into six equal groups and each group with 30 patients; each group given intrathecally the standard dose of 2.5 ml of 0.5% hyperbaric bupivacaine along with 0.5 ml (25 µg) each of dexmedetomidine clonidine and neostigmine and parameters of intraoperative and the post-operative period was recorded. Eachpatient was assessed for effective analgesia in operation, and presence of complications (nausea, vomiting, sedation and pruritus) visual analogue pain score (VAS) postoperatively by a blinded investigator inthe post-anesthesia care unit (PACU).

Results:

The postoperative analgesia is more effective with Group BC (the gold standard) than Group BD, GroupBN and Group B. The various regression parameters were strongly significantly in GroupBC followed by Group BD and Group BN compared to Group B ($p < 0.001$). The maximum sensory levels obtained in study groups

werecomparableandsufficient for the surgery with Peak sensory level was achieved earlier in Group BC (T 5.5 ± 1.2) compared to Group B (68 ± 11.3). The mean time for two segment sensory regression was significantly prolonged in Group BC (149 ± 12.3) compared to Group B (44.15 ± 6.5)($p < 0.001$) The time taken for sensory regression of the blockade to S1 level was more in Group BC (364.5 ± 18.2) compared to Group B (126.3 ±12.4) ($p < 0.001$). 24 hours postoperative VAS scores were consistently low in Group BC (3.59±0.50) compared to Group B (6.81±2.50) ($p < 0.001$). Whereas the time of onset of Bromage Grade 3 min was rapid onset in Group BC (389 ± 39.9) followedby Group BD (362 ± 26.9), Group BN (342.2 ± 11.6) compared to Group B(113.2 ± 11.6) ($p < 0.001$). Both the groups were observed for occurrence of possible adverse effects like nausea, vomiting, pruritus, shivering, hypotension, bradycardia and pain. Incidence of these adverse effects were low and not significant in Group BC, Group BD and Group BN but significant in Group B

Conclusion:
The study outcome concludes that clonidine has rapid onset of sensory and motor blockade succeeded by dexmedetomidine and neostigmine has prolonged sensory and motor blockade with impressive post-operative analgesia. 0.5 ml of 25µg Clonidine along with 0.5% of 2.5 ml hyperbaric bupivacaine in lower abdominal surgeries has major advantages in prolonged and early onset of sensory and motor blockage duration and has better post-operative analgesia when compared to Bupivacaine with neostigmine, Bupivacaine with dexmedetomidine and Bupivacaine alone.

Introduction

The delivery of the infant into the arms of a conscious and pain free mother is one of the most exciting and rewarding moments in medicine[1,2]. It is possible only with ideal anaesthesia which provide comfortable analgesia with adequate muscle relaxation and pain management during pre and post-operative period that can decrease morbidity and mortality[3]. Spinal anaesthesia is most preferable technique for lower abdominal surgeries, caesarean sections etc[4]. Despite plethora of elective procedures use bupivacaine its limitations limited its familiarity. To mitigate these constraints and to extend the pre and post-operative spinal analgesia various other anesthetic agents with good analgesic activities such as clonidine, neostigmine, dexmedetomidine are co-administered as adjuvant with bupivacaine[5-8]. Neostigmine is a quaternary ammonium compound with a strong alkaline carbamoyl group. Neostigmine works as anticholinesterase agent by activating descending pain inhibitory system and effective in decreasing somatic pain[9,10]. Dexmedetomidine, a new highly selective α-agonist approved by Food and Drug Administration (FDA) as a short-term sedative for mechanically ventilated intensive care unit (ICU) patients and used as a neuraxial adjuvant with hyperbaric bupivacaine in spinal anaesthesia for subarachnoid, epidural and caudal blocks due to its stable hemodynamic conditions, good quality of intraoperative and prolonged postoperative analgesia with minimal side effects[11-15]. Clonidine, a selective alpha two agonist agent, routinely used as a premedication for general anesthesia decreases the requirement of analgesics and anesthetic drugs intraoperative. Intrathecal clonidine produces analgesia by indirectly inhibiting the activity of wide dynamic range (WDR) neurons[16]. Due to lack of previous combination study of the selected drugs authors aimed to investigate the efficiency of bupivacaine along with Dexmedetomidine Neostigmine and Clonidine as an Adjuvant.

Materials and methods

A prospective randomized double blind controlled comparative study on 120 parturients between 20 – 35 years age group, scheduled for lower segment caesarean section belonging to ASA class I and II were included in the study to evaluate the efficacy of intrathecal bupivacaine along with the selected drugs in various clinically well-organized combinations with respect to the duration of analgesia and hemodynamic effects was commenced in

Government medical College Aurangabad Maharashtra, India during the period between Mar 2019 and Mar 2022 after obtaining ethical committee clearance as well as informed consent.

The study population was randomly divided into six groups each with 30 patient size after routine pre-anaesthetic examination was conducted before surgery.

Group B - 2.5 ml of 0.5% hyperbaric bupivacaine alone and 0.5 ml of normal saline

Group BC – received 2.5 ml of 0.5% hyperbaric bupivacaine + 0.5 ml 25 µg of clonidine

Group BD - patients received 2.5 ml of 0.5% hyperbaric bupivacaine + 0.5 ml of 25 µg of dexmedetomidine.

Group BN - received 2.5 ml of 0.5% hyperbaric bupivacaine + 0.5 ml of 25 µg of neostigmine

Inclusion criteria

- Parturients aged between 20 to 30 years
- Parturients belonging to ASA class I and II posted for elective lower segment caesarean section, who weighs 50 to 70 kilograms.

Exclusion criteria

- Parturient refusal
- Parturients belonging to ASA class III, IV and V.
- Parturients with comorbid diseases like hypertension, diabetes mellitus and ischemic heart disease.
- Parturients posted for Emergency surgeries.
- Morbidly obese parturients.
- Parturient whose height less than 150cms.
- Parturients having:
  - raised intracranial pressure
  - severe hypovolemia
  - bleeding coagulopathy
  - local infection

Results

The parturient participants in all groups were comparable with respect to demographic characteristics (table 1). Sensory and motor blockade characteristics are shown in Table 2. The various regression parameters were strongly significantly in Group BC followed by Group BD and Group BN compared to Group B ($p < 0.001$).

Table 1: Demographic characteristics

Variable	Group B	Group BC	Group BD	Group BN	P value
Mean Age (y)	24.6 ± 2.9	25.2 ± 3.8	22.21 ± 3.80	24.35 ± 4.08	0.45
Mean Weight (kg)	61.7 ± 6.3	59.8 ± 5.6	56.7 ± 6.3	60.8 ± 5.6	0.95
Mean Height (cm)	155.9 ± 4.4	156.3 ± 4.5	149.9 ± 4.4	152.3 ± 4.5	0.73
Mean BMI (kg/m^2)	25.6 ± 2.1	24.4 ± 2.9	24.6 ± 2.6	24.4 ± 2.9	0.82
ASA score I and II ratio	20:10	22:8	18:12	21:9	>0.05

The maximum sensory levels obtained in study groups were comparable and sufficient for the surgery with Peak sensory level was achieved earlier in Group BC (T 5.5 ± 1.2) followed by Group BD (T 5.9 ± 1.5), Group BN (T 6.01 ± 1.9) compared to Group B (T 7.9 ± 1.4) ($p = 0.001$). The time for analgesia onset was significantly rapid in Group BC (33 ±11.3) followed by Group BD (40 ±11.1), Group BN (45 ± 10.9) compared to Group B (68 ± 11.3) ($p = 0.001$

Table 2: Comparative block characteristics in two groups

Repression parameters	Group B	Group BC	Group BD	Group BN	P value
Time for onset of analgesia (sec)	68 ± 11.3	33 ±11.3	40 ±11.1	45 ± 10.9	< 0.001
maximum sensory level	T 7.9 ± 1.4	T 5.5 ± 1.2	T 5.9 ± 1.5	T 6.01 ± 1.9	0.001
Time to peak sensory level (min)	4.98 ± 1.6	3.98 ± 1.6	4.15 ± 1.7	4.29 ± 1.9	0.023
Time for two segment sensory regression (min)	44.15 ± 6.5	149 ± 12.3	141 ± 12.3	139.15 ± 6.5	< 0.001
Time taken for sensory regression to S1 (min)	126.3 ±12.4	364.5 ± 18.2	361 ± 14.2	358.3 ±11.4	< 0.001
Duration of analgesia (min)	68.9 ± 11.1	432.3 ± 84.6	421.2 ± 31.6	416.9 ± 51.1	< 0.001

Regression to Bromage 0 (min)	71.25± 11.3	45 ±11.3	48.6 ± 2.8	52.6 ± 1.8	< 0.001
Onset to Bromage 3 (min)	113.2 ± 11.6	389 ± 39.9	362 ± 26.9	342.2 ± 11.6	< 0.001
VAS score	6.81±2.50	3.59±0.50	4.01±1.50	4.16±2.20	<0.001

The mean time for two segment sensory regression was significantly prolonged in Group BC (149 ± 12.3) followed by Group BD (141 ± 12.3), Group BN (139.15 ± 6.5) compared to Group B (44.15 ± 6.5)($p < 0.001$). The time taken for sensory regression of the blockade to S1 level was more in Group BC (364.5 ± 18.2) followed by Group BD (361 ± 14.2), Group BN (358.3 ±11.4) compared to Group B (126.3 ±12.4) ($p < 0.001$). 24 hours postoperative VAS scores were consistently low in Group BC (3.59±0.50) followed by Group BD (4.01±1.50), Group BN (4.16±2.20) compared to Group B (6.81±2.50) ($p < 0.001$). The mean duration of analgesia was recorded more in Group BC (432.3 ± 84.6) followed by Group BD (421.2 ± 31.6), Group BN (416.9 ± 51.1) compared to Group B (68.9 ± 11.1) ($p < 0.001$). The time of onset of Bromage Grade o min was rapid in Group BC (45 ±11.3) followed by Group BD (48.6 ± 2.8), Group BN (52.6 ± 1.8) compared to Group B (71.25± 11.3)($p < 0.001$). Whereas the time of onset of Bromage Grade 3 min was rapid onset in Group BC (389 ± 39.9) followed by Group BD (362 ± 26.9), Group BN (342.2 ± 11.6) compared to Group B (113.2 ± 11.6)($p < 0.001$).

Table 3 – Adverse effects

Adverse effect	Group B	Group BC	Group BD	Group BN	P value
Nausea	**8 (26.66%)**	**2 (6.66%)**	**8 (26.66%)**	**9 (30%)**	**0.001**
Vomiting	**3 (10.1%)**	**2 (6.66%)**	**3 (10.1%)**	**5 (16.66%)**	**0.05**
Pruritus	**4 (13.33%)**	**0 (0%)**	**1 (3.33%)**	**1 (3.33%)**	**0.05**
Hypotension	8 (26.66%)	0(0%)	0 (0%)	0 (0%)	1
Shivering	0 (0%)	1 (3.33%)	0 (0%)	0 (0%)	.32
Bradycardia	5 (16.66%)	2(6.66%)	0 (0%)	0 (0%)	1
Pain	0 (0%)	1 (3.33%)	1 (3.33%)	2 (6.66%)	0.07
Total	28 (93.33%)	8 (26.66%)	13 (43.33%)	17 (56.66%)	0.17

The incidence of adverse effects varies among observable groups (table 3). Both the groups were observed for occurrence of possible adverse effects like nausea, vomiting, pruritus, shivering, hypotension, bradycardia and pain. Incidence of these adverse effects were low and not significant in Group BC, Group BD and Group BN but significant in Group B.

Discussion

The combined use of these three drugs along with hyperbaric bupivacaine for cesarean delivery has not been extensively studied hence, the present trial was conducted to study the efficacy of addition of dexmedetomidine, clonidine and neostigmine in various combinations to intrathecal hyperbaric bupivacaine for elective LSCS. Lower abdominal surgeries are performed under spinal anaesthesia is feasible but it has limited period of postoperative analgesia. Intrathecal bupivacaine alone has minimal duration of post-operative analgesia; with intrathecal adjuvants the duration of analgesia will prolong. This study was designed to assess the efficacy of 0.5% hyperbaric bupivacaine alone, 0.5% hyperbaric bupivacaine with 25µg neostigmine and 0.5% hyperbaric bupivacaine with 25µg clonidine and 0.5% hyperbaric bupivacaine with 25µg dexmedetomidine. From our study results it is conformed that the

Author	Year	Sample size	Conclusion
Poupak Rahimzadeh et al [17]	2018	90	Using dexmedetomidine as an adjuvant to bupivacaine for spinal anesthesia in lower limb surgeries has longer duration of sensory and motor block and longer postoperative analgesia.
T. Senthil Kumar et al[18]	2021	120	The combination of clonidine with fentanyl increased the intraoperative analgesic efficacy and significantly prolonged postoperative analgesia compared with clonidine alone. Stable Intra Operative hemodynamics was obtained. The duration of analgesia was prolonged. The incidence of side effects due to additive effects of the drugs was minimal. The fetal outcome was not altered.
Elsayed Mohamed Abdelzaam et al[19]	2019	100	Bupivacaine clonidine, bupivacaine neostigmine, and bupivacaine fentanyl intrathecal anesthesia produced a longer duration of postoperative analgesia after lower abdominal surgery in patients than bupivacaine alone. Bupivacaine clonidine mixture had the most extended period of analgesia, but with hypotension. So bupivacaine fentanyl mixture with moderate duration of analgesia and minimal side effects is most safe for a patient.

intrathecal administration of bupivacaine along with various adjuvants has increased the desired effects amongst all studied combinations bupivacaine along with clonidine has produced more pronounced effects followed by combinations with dexmedetomidine and neostigmine respectively (table 2).

Conclusion

The study outcome concludes that clonidine has rapid onset of sensory and motor blockade succeeded by dexmedetomidine and neostigmine has prolonged sensory and motor blockade with impressive post-operative analgesia. 0.5 ml of 25µg Clonidine along with 0.5% of 2.5 ml hyperbaric bupivacaine in lower abdominal surgeries has major advantages in prolonged and early onset of sensory and motor blockage duration and has better post-operative analgesia when compared to Bupivacaine with neostigmine, Bupivacaine with dexmedetomidine and Bupivacaine alone.

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