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A comparison of fetomaternal outcome in PCEA using fentanyl, clonidine and dexmedetomidine as adjuvants with Ropivacaine in painless labor: a prospective, double blinded randomized study

A. Kumar (*), Reena (**)

Abstract : *Background* : Patient controlled epidural analgesia has been associated with marked maternal satisfaction. Combination of local anesthetics with various adjuvants have been tried to ensure optimum analgesia with no or negligible fetomaternal side effects.
Aim: To compare fentanyl, clonidine or dexmedetomidine as adjuvants with ropivacaine for labor epidural analgesia (LEA) using a PCEA pump with the objective to assess fetomaternal outcome in terms of analgesic effect, success rate of vaginal delivery, complications, neonatal APGAR score and maternal satisfaction.
Materials and methods : Sixty full term laboring women received 10 ml 0.2% ropivacaine followed by continuous infusion of 0.1% ropivacaine with 2 µg/ml of either dexmedetomidine, fentanyl or clonidine respectively in Groups A, B, and C at 6 ml/hr. demand bolus setting was 2 ml with a lock out interval of 15 minutes. At full cervical dilatation another 10 ml bolus of respective solution were given. Parturients were monitored at 0, 10, 20, 30 min after giving 1st epidural bolus dose and then at 30 min interval for ongoing labor for pain relief (VAS), motor blockade (Bromage score), progress of labor (duration of 1st stage and 2nd stage), mode of delivery, fetal APGAR score (at 1 min and 5 min), vitals (HR, NIBP, RR, SpO2), overall patient satisfaction and complications. The statistical analysis was done both qualitatively (Fisher-exact test/Chi-square test) and quantitatively (one-way analysis of variance test with post-hoc intergroup comparisons using Bonferroni's correction).
Results : Onset of pain relief was earlier in fentanyl group, however after 1 h all three groups showed comparable pain relief ($P>0.05$). There was a significant reduction in HR in group C and B compared to group A ($P<0.001$) and MAP in group C compared to groups A and B. The motor-blocking potency was slightly higher in dexmedetomidine group, however no significant motor weakness observed in any parturient. Mean demand bolus need was more in group C compared to A and B ($P<0.001$). There was no significant difference in mode of delivery (either SVD or cesarean) in between the groups. There was not a single case of fetal distress and most of the parturients showed satisfactory response to PCEA.
Conclusion : All three study drugs produced equipotent analgesia in combination with ropivacaine 0.1%. There was absolute pain relief without significant motor blockade or any increase in instrumentation/cesarean deliveries or any adverse fetal outcomes.

Key words : PCEA ; labor analgesia ; Fentanyl ; Clonidine ; Dexmedetomidine.

Introduction

Childbirth is a natural experience of the majority of healthy married women in our society. Naturally, this experience should be joyful and delightful. Therefore maternal request is sufficient justification for pain relief during labor. Among various modalities available, Neuraxial labor analgesia is the gold standard of pain relief during childbirth (1). Recent advancements in the (2, 3) techniques and availability of newer drugs and adjuvants have made it a very effective procedure with minimal or no side effects. Various studies in the past few decades have evaluated role of opioids or alpha-2 agonists as adjuvants in central neuraxial blockade. But only a few have analyzed their efficacy in labor epidural analgesia.

Opioids like fentanyl have been successfully used as an adjunct for epidural administration along with lower doses of local anesthetics to provide optimum analgesia (4, 5). The opioid not only have a dose sparing effect on local anesthetic but also provide superior analgesia. However, side effects like nausea, vomiting, pruritus, urinary retention, and respiratory depression can occur occasionally (6, 7).

Amit Kumar, MD ; Reena, MD.
(*) Department of Anesthesiology, SGPGI, Lucknow, India.
(**) Department of Anesthesiology, Heritage Institute of Medical Sciences, NH-2, Bhadwar, Varanasi, India.
Corresponding author : Dr. Reena, Department of Anesthesiology, Heritage Institute of Medical Sciences, NH-2, Bhadwar, Varanasi-221311, India. Tel.: 0542-7111071
E-mail : reena216@gmail.com

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Clonidine and dexmedetomidine are α-2 adrenergic agonists which potentiate the action and duration of local anesthetic drugs when epidurally administered (8, 9). They act on central nervous system as well as pre and post synaptic sympathetic nerve terminals, thereby decrease the sympathetic outflow and nor-epinephrine release causing sedative, anti-anxiety, analgesic, sympatholytic and hemodynamic effects (10-12).

Recent advances in the field of anesthesia have made epidural analgesia more effective with minimal side effects and researches are still going on to create new dimensions to this method. Introduction of PCEA pump is one of them , it does not only allow continuous administration of drug into the epidural space but also covers differences in anesthetic requirement as patient can match dose of analgesia to amount of pain as labor progresses. Also it reduces the need of clinical top-ups which in total decreases the amount of drug given and thus decreases the possibility of motor block. However this may be costly and the woman requires instructions to use the PCEA pump so patient should be willing enough to use it.

In the present study, we used fentanyl, clonidine or dexmedetomidine as adjuvants with ropivacaine for labor epidural analgesia (LEA) using a PCEA pump with the objective to assess fetomaternal outcome in terms of analgesic effect, success rate of vaginal delivery, complications, neonatal APGAR score and maternal satisfaction.

Materials and Methods

The Institutional ethical committee approval was taken and 60 ASA physical status I and II parturients at term, with spontaneous onset of labor requesting epidural analgesia were enrolled after obtaining written informed consent, into this prospective, double-blinded, randomized sequential-allocation study. Inclusion criteria were patients willing to have painless delivery**,** parturients with vertex presentation**,** patient in active phase of labor (≥3 cm dilatation)**,** without fetal distress prior to the procedure. Patient having severe cardiac disease**,** morbid obesity**,** patient having spinal deformities**,** multipara patients (>= 3 children), patient having bleeding disorders or anemia and those not willing to participate were excluded.

The procedure was explained to the patients. All were prehydrated with 500 ml of lactated ringer's solution over 10-15 minutes through a wide bore IV cannula. Patients were positioned in left lateral decubitus/sitting position according to the suitability for the block and the part was cleaned with spirit and betadine lotion and draped. The interspace L3-4 was locally infiltrated with xylocaine 2%. 18 G Tuohy's needle was inserted via midline approach. Epidural space was identified using loss of resistance technique and a multi orifice catheter was introduced 5 cm in the space in cephalic direction. The test dose of xylocaine 2% with adrenaline was given after confirming negative aspiration for blood and CSF. The epidural catheter was placed before the active phase of labor because the patients were more comfortable and easily positioned or in active labor when cervical dilatation ≥ 3cm. Drugs were given only after the labor was well established.

The participants were allocated randomly into one of the following groups based on a computer generated sequence provided in sealed envelopes. The drugs used in PCEA pump for continuous infusion in 3 groups were :

Group A = PCEA solution of Ropivacaine 0.1% with Dexmedetomidine 2 µg/ml.

Group B = PCEA solution of Ropivacaine 0.1% with Fentanyl 2 µg/ml.

Group C = PCEA solution of Ropivacaine 0.1% with Clonidine 2 µg/ml.

When labor was well established and was progressing well i.e. regular contractions 3-4 minutes apart and lasting about, 1 minute, cervical dilatation 3-4 cm and Fetal head was well engaged, 10 ml bolus of 0.2% ropivacaine alone was given in incremental fashion to all parturients and then connected with their respective PCEA solution. PCEA pump setting was continuous basal infusion @ 6ml/h and 2ml of demand bolus with a 15 min lock out interval.

In second stage (at full cervical dilatation) 10 ml bolus of the respective solution was given in sitting position (perineal dose) which helped in episiotomies or any other operative delivery and PCEA was continued up to the completion of delivery. Uterine displacement was maintained continuously and each parturient was encouraged to turn from side to side or even move around if required during labor. An anesthesiologist who was unaware of the dose or drugs given, performed all assessments and data recordings. All the parturients were monitored continuously for pain relief, progress of labor, hemodynamic changes, respiratory rate, Spo2 and drug side effects at 0, 10, 20, 30 min after giving 1st epidural bolus dose and then at 30 min interval for ongoing labor.

Pain was assessed using 10 cm linear visual analogue scale (VAS) at the peak of uterine con-

tractions and then at mentioned intervals. Sensory block level was assessed with changes to cold sensation while motor block was assessed using six point modified Bromage score : 1- Complete block i.e. Unable to move feet or knees, 2 -Almost complete block i.e. Able to move feet only, 3-Partial block i.e. just able to move knees, 4- Detectable weakness of hip flexion while supine with full flexion of knees, 5- No detectable weakness of hip flexion while supine, 6- Able to perform partial knee bend. Bromage score > 4 was considered adequate as it signified minimum motor blockade which is ideal for labor analgesia. Other maternal monitoring included NIBP, HR, SpO2, ECG and cervical dilatation at the entry of study, duration of first stage and second stage of labor and mode of delivery. Occurrences of side effects like hypotension, bradycardia, nausea-vomiting, pruritus, sedation or shivering were also recorded and managed according to standard protocol.

Fetal monitoring was done using a cardio tocograph by an obstetrician blind to the study drugs used. The monitoring started 30 minutes prior to epidural placement and continued till the delivery. Neonatal APGAR scoring was done and analyzed at 1 minute and 5 minutes after delivery.

Parturients' satisfaction was assessed using a four-point scale (0 = Totally dissatisfied, 1 = Moderately dissatisfied, 2 = Reasonably satisfied, 3 = Totally satisfied with pain relief) (13).

A minimal sample size of 20 parturients was found necessary for each group based on a previous study and considering 95% confidence interval and 80% power of study and adding for contingency of 10% (14). Statistical analysis of data was performed using SPSS version 16.0. Parameters including total duration of labor, total study drug requirements, pulse rate, blood pressure were compared by one-way analysis of variance with Post hoc intergroup comparisons using Bonferroni's correction. Nominal data including mode of delivery, need of demand boluses and side effects were compared by Fischer's exact test/Chi-square test whichever is applicable. The critical value of "p" indicating the probability of significant difference was taken as <0.05 for comparisons.

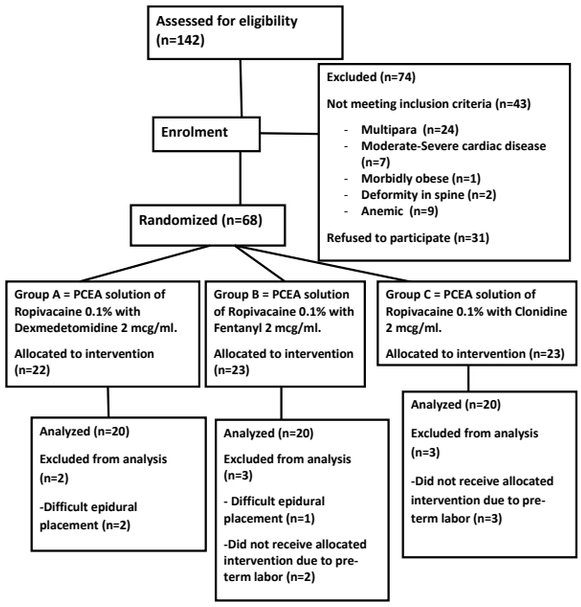

Fig. 1. — Study Design.

Results

A total of 142 parturients were assessed for eligibility, out of which 74 were excluded during enrolment as they did not fulfill the inclusion criteria. The study design is shown in figure 1. Final analysis included sixty parturients, 20 in each group; all of them successfully completed the study with no drop outs. All three groups were comparable in terms of demographic profile, gestational age, preoperative cervical dilatation and durations of first and second stages of labor (Table 1).

Significant reduction is seen in VAS score after 20 min of putting patient on PCEA (P<0.05). When compared VAS score was significantly reduced in group B as compared to group C, comparisons among the other groups were not significant. After 1 h the overall analgesia in three groups was

Table 1

Demographic data and progress of labor

	Group A	Group B	Group C	P value
Age (yrs)	23.70 ± 2.20	23.45 ± 3.19	22.96 ± 3.72	>0.05
Weight (kg)	51.80 ± 2.85	52.40 ± 2.85	52.11 ± 3.36	>0.05
Gestational age (weeks)	39 ± 1.6	39 ± 1.7	39 ±1 .5	>0.05
Mean Cervical dilatation (cm)	4.150 ± 0.73	4.075 ± 0.84	3.95 ± 0.81	>0.05
Duration of first stage of labor (h)	5.25 ± 1.106	4.95 ± 1.234	5.70 ± 1.720	>0.05
Duration of second stage of labor (min.)	50.50 ± 9.445	49.50 ± 14.681	42.50 ± 12.085	>0.05

Values are presented as mean ± SD.

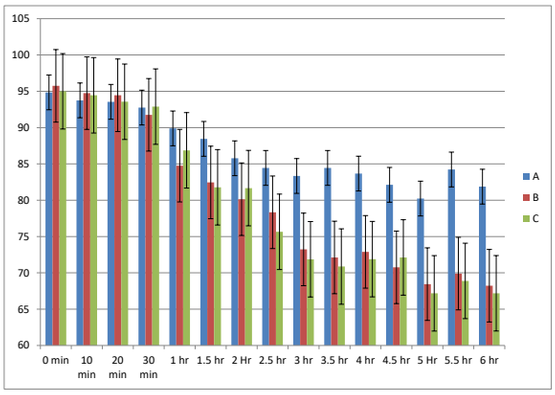

Fig. 2. — Comparison of Mean Maternal Heart rate (HR).

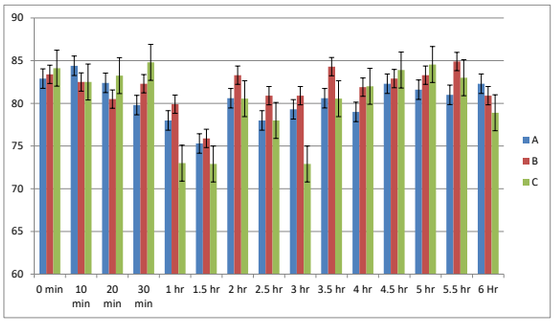

Fig. 3. - Comparison of Maternal Mean arterial pressure (MAP).

satisfactory as each of them shows a significant reduction in VAS score.

There was a significant reduction in HR in group C and B compared to group A (P<0.001) and MAP in group C compared to Groups A and B, however none of the parturients developed bradycardia requiring atropine (Figure 2 and 3). Hypotension (fall in MAP > 20% of baseline values) was seen in 1 and 4 parturients in groups A and C respectively (Table 4) and managed by fluids bolus and inj. Ephedrine 6 mg boluses.

The number of demand boluses required in group C was comparatively more (Table 3) as compared to the mean number of demand boluses in other two groups. The difference in the three groups is statistically significant with lowest demand boluses required in group B as compared to group A and C.

Table 2

Visual Analogue Scale (VAS)

	Group A	Group B	Group C	f value	P value
Pre-epidural	7.15 ± 1.387	7.75 ± 1.585	7.60 ± 1.046	1.058	0.354
10 m	6.20 ± 1.056	6.05 ± 1.356	6.80 ± 0.951	2.448	0.096
20 m	5.35 ± 1.089	4.50 ± 1.100	6.05 ± 1.356	8.532	0.001*
30 m	3.50 ± 0.889	2.85 ± 0.813	3.45 ± 1.356	2.386	0.101
1 h	2.40 ± 0.754	2.65 ± 0.745	2.85 ± 0.988	1.452	0.243
1.30 h	2.25 ± 0.639	2.70 ± 0.801	2.30 ± 1.031	1.727	0.187
2 h	2.30 ± 0.571	2.10 ± 0.553	2.05 ± 0.759	0.869	0.425
3 h	2.15 ± 0.489	2.10 ± 0.553	2.50 ± 0.946	1.980	0.147
3.30 h	2.25 ± 0.639	2.30 ± 0.811	2.40 ± 0.132	0.358	0.700
4	2.10 ± 0.551	2.20 ± 0.543	2.05 ± 0.752	0.302	0.740
4.30 h	2.25 ± 0.469	2.20 ± 0.593	2.20 ± 0.949	0.034	0.965
5 h	2.50 ± 0.888	2.15 ± 0.823	2.45 ± 0.352	1.370	0.262
5.30 h	2.35 ± 0.089	2.40 ± 0.100	2.25 ± 0.356	2.519	0.089
6 h	2.15 ± 0.389	2.25 ± 0.587	2.20 ± 0.045	0.310	0.734

Data expressed as mean ± SD. * P <0.05

The delivery pattern of the 60 cases in this series is compared. Total 53 parturients (91.6%) had spontaneous vaginal delivery in which 2 parturients (3.3%) had instrumental delivery (forceps or ventouse assistance). There were five parturients (8.3%) who ultimately needed cesarean sections. However, there was no significant difference in mode of delivery either SVD or cesarean in all the groups. It was also observed that of all the vaginal deliveries (spontaneous or assisted) (n=55), 32 parturients required episiotomies. All 60 parturients had received the perineal dose just prior to full dilatation and thus they required no additional analgesia or local anesthetic for episiotomy. Parturients were also very comfortable post delivery. Maternal satisfaction was high and comparable in all the three groups (Table 3).

There are group specific side effects seen in the different study groups like incidence of pruritus and nausea was more in fentanyl group (0 vs 4 vs 0 and 0 vs 1 vs 0 parturients respectively for groups A, B and C) whereas hypotension and shivering was seen mostly in clonidine group (1 vs 0 vs 4 and 0 vs 0 vs 2 parturients respectively for groups A, B and C), and vomiting was the complaint mainly in dexmedetomidine group (3 vs 0 vs 1 parturients for

Table 3

Demand boluses, mode of delivery and maternal satisfaction

	Group A	Group B	Group C	Fvalue	P value
Mean no. of demand boluses	3.40 ± 0.94 (3-6)	2.35 ± 0.58 (1-3)	5.45 ± 1.05 (1-5)	64.219	<0.001*
Mode of delivery Vaginal/forceps, assisted/Cesarean (%)	85/05/10	95/0/05	85/05/10	NS	>0.05
Maternal satisfaction 0/1/2/3 (%)	0/5/15/80	0/5/5/90	0/10/20/70	NS	>0.05

Values are presented as range, mean ± SD or as percentages. * P value <0.05

Table 4

Maternal side effects

Side effect vs. group	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
nausea	0	0	1	5	0	0
vomiting	3	15	0	0	1	5
pruritus	0	0	4	20	0	0
hypotension	1	5	0	0	4	20
shivering	0	0	0	0	2	10
Bromage score < 3	3	15	2	10	2	10

Data are expressed as No. and percentages.

groups A, B and C respectively), so in these terms the p-value is significant but if we see the percentage of these side effects none of these occurred in more than 20% parturients of that group which is very less to label a drug inappropriate to be used as an adjuvant. Most of the parturients retained adequate motor power during the entire period of observation as seen in table 4.

There was no case of fetal distress during first stage or second stage of labor in all the three groups. There was not a single case of newborn where APGAR score was less than 7 at 5 minutes. There were 5 babies who had APGAR score of 7 at one minute. They improved after suctioning and giving oxygen through a mask. The subsequent APGAR scores at 5 minutes were 9/10 in all the newborns. Subsequently after delivery none of the babies had any problem in the ward and till discharge.

Discussion

Epidural analgesia has long been used to produce analgesia for labor and delivery using various local anesthetics (LA) in combination with an adjuvant. It is the most common method applied for combating pain during delivery. In this study, we used ropivacaine because it has been known to cause less motor weakness by the epidural route while still providing effective analgesia(15, 16). Owen et al. showed that fentanyl 2 µg/ml when added to 0.1% ropivacaine the analgesia was improved to a quality almost equal to 0.2% ropivacaine (17). Fentanyl has been successfully used with various concentrations of LA, and has shown to reduce the overall requirements of LA, while potentiating and prolonging their effects. However associated side effects have promoted search of non-opioid adjuvants which can provide optimum analgesic effect in combination with LA drugs while have no or negligible fetomaternal side effects.

Parker et al used clonidine 5 µg·ml-1 with bupivacaine 0.0625% and found increased duration of LEA without a clinically significant increase in side effects (18). Dexmedetomidine is a highly selective a-2 adrenergic agonist with an affinity of eight times greater than clonidine (19). Epidural administration of dexmedetomidine for the purpose of labor analgesia has been studied by a few authors only (20). In our knowledge this is the first study evaluating role of dexmedetomidine in combination with ropivacaine and compared to fentanyl and clonidine in terms of fetomaternal outcome in patient controlled labor epidural analgesia.

Topcu I. et al observed that combination of fentanyl or clonidine with local anesthetics produces similar and prolonged analgesia as compared to local anesthetics alone (21). We did not include any control group as use of local anesthetics without any adjuvant for labor epidural analgesia is nowadays an uncommon practice. Significant reduction was seen in VAS score after 20min of putting parturient on PCEA ($P<0.05$). When compared VAS score was significantly reduced in fentanyl group as compared to clonidine group after 20 min. The overall analgesia in three groups was satisfactory as each of them showed a significant reduction in VAS score. Pain relief as assessed subjectively by the parturients was nearly equal for all the groups. None of the parturients complained poor or no analgesia in any of the groups as seen by the mean VAS score after 20mins, which was significantly reduced ($p=0.001$), showing the effect of the epidural infusion. The mean VAS score after 30 min was in range 2-3, 3-3.5, 3-3.5 respectively among the fentanyl, clonidine and dexmedetomidine groups which further reduced after 1h during the course of labor.

Motor block was assessed by the Modified Bromage score. None of the parturients in any group observed significant motor block, the reason being low concentration of ropivacaine used, similar to other studies (17). The motor-blocking potency was slightly higher in dexmedetomidine group as compared to other two groups, however the difference was insignificant. There was no significant difference in mode of delivery (either SVD or cesarean) in between the groups. Our results were in support of studies done by Chethanananda et al and Halpern and Walsh (22, 23).

We did not observe statistically significant difference ($p>0.05$) in the duration of active phase of first stage of labor in this study similar to observations by Paech et al. (24) and Lyons et al. (25). Duration of second stage of labor was almost similar in all the groups in our study. Mean duration of second stage of labor was confined between 40-50 min. It has been postulated that a prolonged second stage

Table 5

Neonatal outcome

Apgar score (minute)	Group A	Group B	Group C	Fvalue
1	8.0 ± 0.65	8.05 ± 0.51	8.05 ± 0.69	0.26 (NS)
5	9.0 ± 0.45	9.05 ± 0.51	9.05 ± 0.51	0.13 (NS)

Data are expressed as Mean ± SD. NS : not significant.

of labor may lead to fetal acidosis because of spells of hyper and hypopnea in the mother. Adequate analgesia in laboring patients breaks this spell and thus prevents fetal acidosis.

We observed comparatively more fall in MAP in clonidine group as compared to fentanyl and dexmedetomidine group, however no clinically significant hypotension (> 20% reduction in MAP from baseline value) was seen in any of the groups. Kayaccan et al. reported a contradictory observation of more hypotension in fentanyl group as compared to clonidine group (26). The absence of hypotension in most of the laboring women in our study was probably due to preloading with ringer lactate solution prior to administration of drugs in epidural space and the use of local anesthetic in lower concentration and low doses of study drugs.

There were some specific side effects seen in the different study groups like incidence of pruritus and nausea were more in fentanyl group whereas hypotension and shivering was seen mostly in clonidine group and vomiting was the complaint of some parturients in dexmedetomidine group. Similar findings were noted by others also (25). These side effects were in less than 20 % parturients of specific group, which is very less to label a drug inappropriate to be used as an analgesic adjuvant. None of the parturients reported retention of urine.

There is a wide range of PCEA settings in clinical practice (27). Evidence-based recommendations for an "ideal" PCEA setting is very difficult, given that published studies investigating PCEA for labor analgesia have wide variations in settings, study design and clinical endpoints (28). While some preferred lower PCEA bolus doses other recommended higher dose (29, 30). In our study also we chose small bolus dose of 2 ml with a lock-out period of 15 minutes because of two reasons, first we were using a continuous basal infusion of 6 ml/h, second, we gave an additional bolus of 10 ml of the respective study drugs at full cervical dilatation which provided adequate analgesia for the second stage of labor.

Lastly, all parturients were asked for satisfaction and response regarding technique used (PCEA), pain relief and side-effects. Overall, most of the parturients (90%) showed satisfactory response to PCEA and the satisfaction score was nearly equal in all three groups. The parturients with vomiting were more distressed as compared to others. However all the parturients wanted to receive the same in future pregnancy and would also recommend to other laboring women.

There were few limitations in our study, first we used fixed drug dosing, so effects of higher or lower doses were not studied. However, the doses used in this study were the most commonly used doses in various studies. Second, we did not perform fetal umbilical artery acid base assessment, due to lack of fast track facility for it. Nevertheless, APGAR scoring at 1 and 5 minutes gives adequate information about neonatal well being.

Conclusion

We observed that pain relief as assessed subjectively and objectively were nearly equivalent in all the three groups. However the onset of pain relief was earlier in fentanyl group as compared to the dexmedetomidine and clonidine group. The parturients were able to ambulate with support and didn't complain of marked weakness or inability to move. There was no increase the incidence of forceps delivery or the incidence of cesarean section or adverse neonatal outcomes. Nausea and pruritus was more in fentanyl group while hypotension and shivering was seen mostly in clonidine group. None of the baby required resuscitation. Overall, most of the parturients (93.33%) showed satisfactory response to PCEA and also wanted to receive the same in future pregnancy and would recommend to other laboring women.

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