Comparison of Bupivacaine-Clonidine and Bupivacaine-Fentanyl for postoperative lumbar epidural analgesia

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ABSTRACT

Background: Different adjuvants are co-administered with local anesthetics to improve the speed of onset, duration of analgesia and to reduce the dose; the selection of which is often left to the choice of anesthetist.

Aim: The aim of the study was to compare the analgesic efficacy and the safety profile of clonidine and fentanyl as an adjuvant to bupivacaine for postoperative lumbar epidural analgesia.

Materials and methods: It was a prospective double blind randomized controlled single centre study. It comprised 46 patients of ASA-I-II aged 40-55 years who underwent vaginal hysterectomy. They were randomly allocated in two groups to receive 10ml of 0.125% bupivacine with 50µg clonidine or 10ml of 0.125% bupivacine with 50 µg fentanyl for postoperative epidural analgesia. Patients were observed for analgesic profile and side effects. Statistical analyses were performed by using SPSS 16. Power analysis was based on one-tailed calculations, but all subsequent analyses were two-tailed.

Results: The quality of postoperative analgesia of bupivacaine-clonidine was equivalent to bupivacaine-fentanyl. Side effects such as nausea/vomiting and pruritus were significantly less with bupivacaine-clonidine than bupivacaine-fentanyl.

Conclusion: Clonidine is an effective and safe alternative to epidural fentanyl for postoperative analgesia.

Key words: bupivacaine, clonidine, fentanyl, vaginal hysterectomy, lumbar epidural, post-operative analgesia

INTRODUCTION

Adjuvants are co-administered with local anesthetics to improve the speed of onset, duration of analgesia and to reduce the dose thereby eliminating quite a few side effects associated with larger doses.[1] Epidural fentanyl has been widely used in neuraxial blockades. Its main site of action is substantia gelatinosa in dorsal horn of spinal cord, where it blocks the neural fibers carrying pain impulses, both at pre-synaptic and post synaptic levels.[2]

Clonidine can provide pain relief by an opioid independent mechanism as it directly stimulates pre- and postsynaptic 2-adrenoceptors in the dorsal horn gray matter of spinal cord, thereby inhibiting the release of nociceptive neurotransmitters.[2] Clonidine does not have respiratory depressant effects and the incidence of vomiting and pruritus is less frequent compared with epidural opioids.[3] Furthermore, studies have demonstrated that clonidine is twice potent epidurally than intravenously.[4]

The attempts made earlier for dose determination concluded that 75 µg of clonidine is the optimal epidural dose when added to bupivacaine for operative purposes; smaller doses were not serving the purposes of adequate analgesia, and larger doses were associated with bradycardia, hypotension, sedation and other side effects.[2] Since the present study was designed for postoperative epidural analgesia, we used a smaller epidural top up dose of 50µg clonidine and compared it with 50µg fentanyl as used in previous studies.[2,5]

The primary aim of this study was to determine whether the combination bupivacaine-clonidine has the same analgesic efficacy as that of bupivacaine-fentanyl. We also intend to test the hypothesis that epidural clonidine decreases the incidence of side effects. To eliminate possible confounding factors, such as type of incision or operation that could affect the incidence of pain and side effects, we chose to restrict the study only to patients undergoing a vaginal hysterectomy, in which a lumbar epidural catheter was placed for postoperative analgesia. We thus compared the combination of 50µg clonidine and 0.125% bupivacaine with 50µg of fentanyl and 0.125% bupivacaine administered for postoperative lumbar analgesia.

MATERIALS AND METHODS

After approval from hospital ethical committee 46 women of ASA I & II status aged 40 -55 years requiring elective vaginal hysterectomy were recruited after obtaining informed consent. It was calculated that a sample size of 21 patients per group was required to have 90% power at an α level of 0.05. Considering dropouts, 23 patients were randomized in each group. Power analysis was based on one-tailed calculations, but all subsequent analyses were two-tailed.

Patients with history of hypertension, heart blocks, bleeding or coagulation test abnormalities, psychiatric diseases, diabetes, history of drug abuse and allergy to local anesthetics of the amide type or any contraindication to epidural administration were not considered for the study.

Preoperatively, all the patients were briefed about visual analogue pain scores (VAPS, 0–100 mm scale: 0 = no pain, 100 = worst pain ever). They were given oral alprazolam 0.25mg the night preceeding surgery. All patients were given epidural anaesthesia - diluted solution of 0.5% bupivacaine plain in 5ml incremental boluses.

After surgery, patients were randomly allocated to one of the two groups of 23 each according to a computer generated randomized table. They received epidural top up of either 10ml of 0.125% bupivacine plain with 50 µg clonidine (Group GC) or 10ml of 0.125% bupivacine plain with 50 µg fentanyl (Group GF). The randomization code was maintained in sequentially numbered opaque envelopes until just before use.

The patient's pain intensity was assessed at arrival, marked as VAPS score at 0 hrs. Epidural analgesia was given when VAPS $\geq$ 40 or when the patient demanded (whichever occurred earlier). When the patient was asleep VAPS was noted as zero. The onset of analgesia was defined as the time from injection of the study medication to the first reduction in pain intensity by at least 10 in VAPS. The duration of analgesia was defined as the time between the onset of analgesia and either a return to baseline VAPS or the time when additional pain medication was requested (whichever occurred first). Rescue analgesia was informed to be given epidurally (if there was no relief in pain even after 30 minutes) comprising of 10 ml of the respective study group solution.

The vital hemodynamic parameters were recorded at 15 min interval for the first hour and then hourly for 24 hrs. The level of sedation was also recorded according to Ramsay sedation scale, and accordingly a score of $\geq$4 was considered sedated.[6] Other side effects like nausea, vomiting, headache, pruritus and respiratory depression, bradycardia, urinary retention and hypotension were also recorded on each time of assessment.

Statistical analyses were performed by using SPSS 16 and included Student's *t*-test, χ^2 tests as appropriate. Data are presented as mean and standard deviation. Values of $P < 0.05$ were considered statistically significant. Power analysis was based on an effect size of 10 mm VAPS between groups.

RESULTS

The two groups were similar regarding demographic (in terms of age, weight and height) characteristics. Onset of analgesia was faster and duration was longer in group GF (Table I) but statistically insignificant. VAPS scores were similar in both the groups at all times of observation during 24 hrs suggesting similar quality of analgesia (Table II). Mean arterial pressure (MAP), heart rate and SPO2 were comparable in both the groups during the entire post-operative period. Incidence of nausea and vomiting was 8.69 % in Group GC and 34.78% in Group GF ($p<0.05$). Sedation was noted in 2 patients of Group GC and in 1 patient of Group GF. Hypotension and respiratory depression were not observed in any patient. The incidence of other side effects was low in both the groups. Two patients in both the groups demanded rescue analgesia and was statistically insignificant ($p>0.05$).

Table 1: Analgesic profile

	Group GC	Group GF	d.f.=degree of freedom,N.S.=notsignificant
Onset(min)	8.64±1.542	7.82±1.723	t-value=1.701, d.f.=44, p-value=0.0960 (N.S.)
Duration(min)	225.43±4.99	228.94±6.98	t-value=1.9619, d.f.=44, p-value=0.0562(N.S.)
Total bupivacaine consumed(mg)	80.24±4.98	78.12±5.51	t-value=1.3689, d.f.=44, p-value=0.1780(N.S.)
Number of rescue analgesic doses	2	2	(N.S.)

Group GC =Group clonidine, Group GF = group fentanyl

Table 2: VAPS scores (Mean ± S.D)

Time (hrs)	Group GC (n=23)	Group GF (n=23)	Df=degree of freedom, NS=non significant
0	22.03±2.650	21.09±2.423	t-value = 1.255, d.f. = 44, p- value = 0.2159 (N.S)
3	24.06±3.463	22.17±3.228	t-value = 1.915, d.f. = 44, p- value = 0.0621 (N.S)
6	18.13±4.215	15.94±3.874	t-value = 1.835, d.f. = 44, p- value = 0.0733 (N.S)
9	20.00±4.568	22.03±4.125	t-value = 1.582, d.f. = 44, p- value = 0.1209 (N.S)
12	23.13±3.450	24.06±3.479	t-value = 0.910, d.f. = 44, p- value = 0.3676 (N.S)
15	20.94±6.987	25.00±6.984	t-value = 1.971, d.f. = 44, p- value = 0.0550 (N.S)
18	25.94±7.456	22.03±7.845	t-value = 1.733, d.f. = 44, p- value = 0.0902 (N.S)
21	22.03±2.650	21.09±2.423	t-value = 1.255, d.f. = 44, p- value = 0.2159 (N.S)
24	22.03±7.788	25.00±7.884	t-value = 1.285, d.f. = 44, p- value = 0.2054 (N.S)

Group GC = Group clonidine, Group GF = Group fentanyl

Table 3: Side effect

Side effects	Group (n=23)	GCGroup GF(n=23)	
Nausea/vomiting	2	8	Chi-sq=4.600, d.f. = 1, p value =0.032(p<0.05)*
Sedation	2	1	Chi-sq=0.357, d.f. = 1, p-value 0.550 (p>0.05)
Dry mouth	3	0	Chi-sq=4.059, d.f. = 1, p-value 0.044 (p<0.05)*
Pruritus	0	4	Chi-sq=4.381, d.f. = 1, p value =0.032(p<0.05)*
Headache	2	1	Chi-sq=0.357, d.f. = 1, p value 0.550 (p>0.05)
Urinary retention	2	1	Chi-sq=0.357, d.f. = 1, p-value 0.550 (p>0.05)

Group GC = Group clonidine, Group GF = Group fentanyl

DISCUSSION

The results of the present study demonstrated that it is possible to decrease the unwanted side effects of epidural fentanyl by replacing it with epidural clonidine. The analgesic effects of the combination bupivacaine-clonidine are equivalent to those of the combination bupivacaine-fentanyl.

Eight out of 23 patients had vomiting in group GF compared to 2 patients in group GC. The difference was both statistically and clinically significant (p<0.05). In a study conducted by Gupta S et al., the combination bupivacaine-clonidine had lesser incidence of nausea/vomiting than the control group of bupivacine.[7] Similar results were obtained in studies comparing epidural clonidine and fentanyl.[2,3,8,9] The extradural opioids are well known for their emetic effect while clonidine has anti-emetic properties when administered orally or intravenously.[9] Several studies have been conducted in adults to examine patients' preferences for outcomes in the postoperative period where it was found that avoiding vomiting is the major priority for adults.[8]

Clonidine produces sympatholysis and reduced blood pressure by its actions in the periphery, brainstem, and spinal cord, which is opposed by direct vasoconstriction from alpha$_2$-adrenergic agonists in the periphery. Epidural clonidine reduces blood pressure more when injected in the upper thoracic space than in the cervical, lower thoracic or lumbar space because of direct inhibition of sympathetic preganglionic neurons in the upper thoracic dermatomes which supply the heart.[1] Blood pressure typically decreases more in hypertensive than in normotensive patients after systemic or epidural clonidine administration, perhaps reflecting increased tonic sympathetic drive in some patients with chronic hypertension.[10] In our study none of the patients experienced hypotension or bradycardia. This could possibly be attributed to smaller doses of clonidine administered and the exclusion of hypertensive patients from our study group.

The incidence of dry mouth was higher with clonidine (p< 0.05) while pruritus was observed more with fentanyl (p< 0.05).The incidence of other side effects was similar and low in both the groups. No patient had respiratory depression probably due to smaller dose of fentanyl used. As the two drugs have an additive effect, the side effects can be further reduced by combining them in lower doses.[10]

Quality of analgesia, as assessed by VAPS, was effective and similar in both the groups comparable to other studies.[3,8] The onset was faster and lasted for longer duration in group GF but it was statistically insignificant and similar to the findings of other studies.[2,11]

CONCLUSION

The results of the present study demonstrated that it is possible to decrease the unwanted side effects of epidural fentanyl by replacing it with epidural clonidine. The analgesic effects of the combination bupivacaine-clonidine are equivalent to those of the combination bupivacaine-fentanyl.

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