International Journal of Medical Anesthesiology

E-ISSN: 2664-3774
P-ISSN: 2664-3766
IJMA 2018; 1(2): 37-41
Received: 15-05-2018
Accepted: 22-06-2018

Dr. Deepa T
Associate Professor, Department of Anesthesiology, Sapthagiri Institute of Medical Sciences and Research Centre, Karnataka, India

Dr. Brijesh GC
Associate Professor, Department of Anesthesiology, Muthukumaran Medical College, Tamil Nadu, India

Dr. Renuka R
Assistant Professor, Sapthagiri Institute of Medical Sciences and Research Centre, Karnataka, India

Corresponding Author:
Dr. Renuka R
Assistant Professor, Sapthagiri Institute of Medical Sciences and Research Centre, Karnataka, India

Comparison of dexmedetomidine v/s buprenorphine as an adjuvant to levobupivacaine in spinal anesthesia for infraumbilical surgeries

Dr. Deepa T, Dr. Brijesh GC and Dr. Renuka R

DOI: https://doi.org/10.33545/26643766.2018.v1.i2a.225

Abstract
Background: There has been a constant research towards the invention of adjuvants to local anesthetics in spinal anesthesia so as to improve the efficacy, minimize the side effects and to provide excellent perioperative analgesia. In this journey, the invention of non-opioid adjuvants to replace the most popular opioid adjuvant has taken a lead role. With this background, in our study we have compared Dexmedetomidine with Buprenorphine as an adjuvant to 0.5% levobupivacaine in spinal anesthesia in patients undergoing infraumbilical surgeries.
Methods: Sixty patients randomly allocated to two groups wherein Group LD received 5 mcg of dexmedetomidine with 15mg of 0.5% Levobupivacaine and Group LB received 75 mcg of Buprenorphine with 15 mg of 0.5% Levobupivacaine.
Results: There was no significant difference in the onset time of sensory and motor block in group LD and group LB. The duration of sensory and motor block is statistically significantly prolonged in Group LD as compared to Group LB. Degree of Sedation was better in Group LD when compared with Group LB. Hemodyanamic stability was preserved in both the groups. The time for first rescue analgesia was significantly prolonged in Group LD compared to Group LB.
Conclusion: Dexmedetomidine as an adjuvant to 0.5% levobupivacaine in spinal anesthesia produces longer duration of sensory and motor block but takes slightly more time to attain complete motor block as compared to Buprenorphine. Dexmedetomidine also provides an additional benefit of providing conscious sedation with fewer side effects.

Keywords: Spinal anaesthesia, levobupivacaine, dexmeditomidine, buprenorphine, infraumbilical, surgery

Introduction
Spinal anesthesia is the most popular anesthesia technique in infraumbilical surgeries due to its simplicity, reliability and cost-effectiveness. However, many a times there is requirement of adding adjuvants to local anesthetics in spinal anesthesia so as to intensify the block in the intraoperative period, to prolong the duration of postoperative analgesia and also to reduce the volume of local anesthetics so as to minimize its adverse effects.
Dexmedetomidine, the d-enantiomer of medetomidine belongs to the imidazole subclass of α_2 receptor agonists and being more selective to α_2 receptor than α_1 receptor has emerged as an wonder drug in anaesthetic armamentarium.
Buprenorphine, a μ receptor partial agonist centrally acting lipid soluble analogue of alkaloid the baine. It has low intrinsic activity and can be safely used in subarachanoid block.
With this in mind, this study was conducted to compare the spinal block characteristics of intrathecal dexmedetomidine with buprenorphine as an adjuvant to 0.5% levobupivacaine spinal anesthesia for infraumbilical surgeries.

Methodology
60 ASA physical Grade 1 or 2 patients aged between 18 - 60years of either gender undergoing elective infraumbilical surgeries under spinal anesthesia were taken up for the study after obtaining approval from the institutional ethical committee. The patients were randomly allocated into two groups of 30 each by using closed cover technique. Randomization was done with computer generated random number sequence. Allocation concealment was done by sequentially numbered opaque envelopes. These were used to

assign randomization on the day of surgery. Before including the patients for the study, all patients were explained about the benefits and the risks associated and a written informed consent was obtained. Patients with contraindication to regional anesthesia, patients on calcium channel blockers, β blockers and with heart blocks were all excluded from the study. After routine preoperative assessment at the patients' waiting room in the operation theatre, baseline readings of the vital parameters were recorded. Intravenous line secured and preloaded with 10 ml/kg of ringer lactate 15 minutes prior to the subarachnoid block.

In the operating room, appropriate equipment for airway management and emergency drugs were kept ready. The horizontal position of the operating table was checked. Patients were shifted to the operating room and positioned.

Non-invasive blood pressure monitor, pulse oximeter and ECG leads were connected to the patient. Preoperative baseline systolic and diastolic blood pressure, mean arterial pressure, pulse rate, respiratory rate and oxygen saturation were recorded. On sitting position, the skin over the back was prepared with antiseptic solution and solution and draped with sterile towel.

Group LD - Patients received intrathecal 3ml 0.5% levobupivacaine (15 mg) with Dexmedetomidine (5µg) diluted in 0.5 ml normal saline.

Group LB - Patients received intrathecal 3ml 0.5% levobupivacaine (15 mg) with Buprenorphine (75µg) in 0.5 ml normal saline.

Total volume of the injected solution was 3.5 ml in both groups.

After skin infiltration with 2% lidocaine, 25G Quincke's needle was inserted at the L3-L4 interspace in the midline. After confirming free flow of CSF, the prepared solution was injected as per the group allocation. The patients were made to lie supine immediately after injection. The sensory level was assessed by pinprick sensation using a blunt 25-gauge needle along the mid-clavicular line bilaterally at three-minute intervals for 30 minutes and then every 15 minutes after. The time to reach T10 dermatome and the maximum sensory level (onset of sensory block) achieved were recorded. Scoring was used to assess sensory effect as 0 = no block, 1 = touch sensation (analgesia) and 2 = no sensation (anesthesia). The motor block was assessed according to the modified Bromage scale (0–3). The onset of motor block (time to reach Bromage score 3) and duration of motor block (time to regression of Bromage score 0) were recorded. In the intraoperative period, vital parameters (HR, SBP, DBP, MBP and SpO2) were recorded after the block at 1 min, 3 min, 5 min, 7 min, 10 min then every 5 min in first hour and every 15 minutes up to 3 hours. On achieving T10 sensory blockade level, surgery was allowed. Hypotension (20% fall in MBP from baseline) was treated with ephedrine 6mg intravenous (IV) bolus and bradycardia (HR<50 beats/min) was treated with atropine 0.6mg IV. The onset and duration of sensory block, onset and duration of motor block and all durations were calculated in relation to the time of subarachnoid block. In cases with failure of sub arachnoid block and conversion to general anesthesia, such patients were excluded from study. In post anesthesia care unit (PACU), pain scores and sedation score were recorded using visual analogue scale (VAS) and Ramsay sedation score (RSS) by nursing staff who were unaware of the group assignment. Initially every 30 minutes for 8 hours, then every 2 hours till 24 hours were recorded. Duration of pain relief (effective analgesia) was defined as the time from spinal injection to the first request for rescue analgesics or VAS was >4. Postoperative analgesic rescue was provided by paracetamol 1g IV. The time to request rescue analgesia (the duration of analgesia) was noted. The patients were shifted from PACU after Bromage score achieved to zero. Any side-effects like nausea, vomiting, bradycardia, hypotension, respiratory depression (RR-8/min) were noted and treated accordingly.

Statistical analysis

We took a sample size of 60 patients with 30 in each group assuming power of study 80% and level of significance 5%.The collected data were analysed by chi square test and results obtained in the form of range, mean and standard deviation. Descriptive statistics was used for describing frequencies, mean and standard deviation. Chi square test was applied for comparing qualitative data and Unpaired Student's test using Bonferroni multiple comparisons' test were applied for comparing quantitative data. Time to first analgesic administration was analysed by Kaplan– Meier survival analysis and logrank test. All the data was analysed using SPSS IBM software version 20 (IBM SPSS Advanced statistics, Chicago, IL, USA). P value < 0.05 was considered statistically significant.

Result

Patient demographic data between the two groups were comparable (Table 1 and 2). The onset time of sensory and motor block in both groups was statistically insignificant (Table 3 and 4). The mean duration of sensory block was shorter in Group LB (332 ± 18.81) when compared with Group LD (502.13 ± 12.27). It was statistically significant (p value < 0.05). The mean duration of sensory block in Group LD is approximately 51% longer than Group LB (Table 5).The mean duration of motor block was shorter in Group LB (298.63 ± 35.79) when compared with Group LD (432.33 ± 12.74). It was statistically significant (p value < 0.05). The mean duration of motor block in Group LD is about approximately 44% longer than Group LB (Table 6).The time of sensory regression to S1 was shorter in Group LB (272.27± 15.39) when compared with Group LD (398.1 ± 6.50). It was statistically significant (p value = 0.048 < 0.05). There was a delay in sensory regression of approx approximately 1/3 times (30%) in Group LD comparing to Group LB (Table 7).

In group LD, 36 patients had Ramsay sedation score ≥3 and 4 patients had <3 Ramsay sedation score. In group LB, 3 patients had Ramsay sedation score ≥3 and 37 patients had Ramsay sedation score <3. Mean sedation score in group LD was 3.82±0.67 and in group LB was 2.07±0.26 which is statistically significant (p = <0.0001) (Table 11). The mean values of HR, SBP, DBP and MAP were comparable between the two groups throughout the intraoperative and postoperative periods (Table 8, 9 and 10).All patients had SpO2 greater than 95% at all the times and did not require additional oxygen in PACU. Two patients in groups LB and five patients in group LD received one dose of ephedrine. Four patients in group LD and two patients in group LB required atropine but statistically insignificant (Table 12). VAS values were <3 observed in both the groups during the whole duration of the surgery and none of the patients required additional analgesics.

Table 1: Age distribution

Age group	Age in years			
	Group LB		Group LD	
	No.	%	No.	%
Below 30 years	6	20	8	26.7
31 – 40	9	30	6	20
41 – 50	6	20	9	30
Above 50	9	30	7	23.3
Total	30	100	30	100
Range	19 – 60 years		18 – 60 years	
Mean	42.33		40.57	
SD	12.88		13.22	
'p' value	0.875 Not significant			

Table 2: Gender distribution

Gender	Group LB		Group LD	
	No	%	No	%
Male	25	83.3	23	76.7
Female	5	16.7	7	23.3
Total	30	100	30	100
'p'	0.752 Not significant			

Table 3: Time of onset of sensory block

Parameter	Time of onset of sensory block (in minutes)	
	Group LB	Group LD
Range	3-4	2-3
Mean	3.47	2.57
SD	0.507	0.504
'p' value	0. 629 Not Significant	

Table 4: Time of onset of motor block

Parameter	Time of onset of motor block (in minutes)	
	Group LB	Group LD
Range	3-5	3-5
Mean	3.83	4.13
SD	0.817	0.78
'p' value	0. 775 Not Significant	

Table 5: Duration of sensory block

Parameter	Duration of sensory block (in minutes)	
	Group LB	Group LD
Range	303-360	480 – 520
Mean	332	502.13
SD	18.81	12.27
'p' value	0. 005 Significant	

Table 6: Duration of motor block

Parameter	Duration of motor block (in minutes)	
	Group LB	Group LD
Range	293-360	413-460
Mean	298.63	432.33
SD	35.79	12.74
'p' value	0. 000 Significant	

Table 7: Time of sensory regression to S1

Parameter	Time of sensory regression to S1 (in minutes)	
	Group LB	Group LD
Range	250-299	389-409
Mean	272.27	398.1
SD	15.39	6.50
'p' value	0. 001 Significant	

Haemodynamic variables

Table 8: Mean arterial pressure

Time interval	LB group (Mean ± SD)	LD group (Mean ± SD)	P value
0 min	81.23 ± 10.45	80.17 ± 10.45	0.963
3 min	80.57 ± 13.35	80.90 ± 10.47	0.089
5 min	75.63 ± 14.47	80.33 ± 13.79	0.854
10 min	78.60 ± 13.71	83.20 ± 12.63	0.897
15 min	75.07 ± 11.96	78.97 ± 12.75	0.337
20 min	81.17 ± 13.09	79.53 ± 13.21	0.780
25 min	79.60 ± 10.83	79.60 ± 10.61	0.958
30 min	74.50 ± 10.86	76.97 ± 11.53	0.406
35 min	82.13 ± 12.96	83.47 ± 11.56	0.222
40 min	77.60 ± 10.93	76.43 ± 11.08	0.663
45 min	78.43 ± 11.50	77.57 ± 12.10	0.503

Table 9: Heart rate

Time interval	LB group (Mean ± SD)	LD group (Mean ± SD)	P value
0 min	78.93 ± 12.21	77.43 ± 9.16	0.035
3 min	81.47 ± 13.37	74.27 ± 9.13	0.000
5 min	80.63 ± 12.79	81.07 ± 11.55	0.360
10 min	78.37 ± 13.96	80.33 ± 11.89	0.769
15 min	77.73 ± 15.92	77.80 ± 12.18	0.083
20 min	79.23 ± 13.13	82.40 ± 13.49	0.806
25 min	79.77 ± 12.05	78.57 ± 12.43	0.668
30 min	80.93 ± 12.50	79.87 ± 12.58	0.684
35 min	79.90 ± 11.72	78.17 ± 11.21	0.584
40 min	79.70 ± 12.15	80.73 ± 11.36	0.442
45 min	77.23 ± 11.98	76.37 ± 11.98	0.874

Table 10: SPO2

Parameter	SPO2	
	Group LB	Group LD
Range	97-100%	97-100%
Mean	98.53	98.43
SD	1.008	1.006
'p' value	0.972 Not significant	

Table 11: Degree of sedation

Parameter	Degree of sedation (Ramsay sedation scale)	
	Group LB	Group LD
Range	1-3	2-3
Mean	1.83	2.40
SD	0.791	0.498
'p' value	0. 018 Significant	

Table 12: Adverse effects

Adverse effects	Group LB		Group LD	
	No	%	No	%
Hypotension	8	27	0	0
Bradycardia	6	20	2	7
Shivering	3	10	0	0
Nausea &Vomiting	3	10	0	0
Total cases with adverse effects	20	67	2	7
Total cases without adverse effects	10	23	28	93
Total	30	100	30	100

Discussion

Even though there are lot of adjuvants, the above mentioned two adjuvants were considered for this study because there were only very few studies in the literature comparing the

benefits and side effects of buprenorphine and dexmedetomidine as adjuvants to levobupivacaine for lower abdominal surgeries. Also, they are pharmacologically different drugs but their effects are similar in terms of hemodynamic stability, onset of sensory and motor block and adverse effects. But these two drugs differ in the clinical effects especially in the duration of sensory and motor block, sensory regression and degree of sedation.

Literature is scarce about use of intrathecal dexmedetomidine and buprenorphine as an adjuvant to spinal anaesthesia. In this study we found that, dexmedetomidine 5 µg supplemented to intrathecal levo-bupivacaine significantly prolonged the duration of postoperative analgesia compared with the addition of buprenorphine 75 µg. Both dexmedetomidine and buprenorphine prolonged duration of sensory and motor blockade and reduced the need of rescue analgesia. It has been found recently that prolonged duration of action of buprenorphine is due to its local anesthetic action.

The lesser side effects in the post-operative period was due to its high lipid solubility. Because of its high lipophilic nature, it diffuses quickly into the neural tissue and decreases the chance of rostral spread.

Another drug in the study, dexmedetomidine which is a specific α2 adrenergic agonist, being used in recent times as an additive to intrathecal hyperbaric bupivacaine to prolong the quality and duration of analgesia. The mechanism for the prolongation of the duration of sensory and motor blockade produced by local anesthetic is not clearly known. It is attributed that α 2 adrenergic agonist acts by binding to post synaptic dorsal horn neurons and to the C-fibres in the pre synaptic region. The prolonged analgesic action of intrathecal α2 agonist is by decreasing the release of C-fibres neurotransmitters and by causing hyperpolarisation of neurons in the post synaptic dorsal horn.

Few studies have been conducted with a higher dosage of buprenorphine. Capogna *et al.*, Mahima gupta *et al.* and Sapkal Praveen S *et al.*, have chosen 60µg of buprenorphine as an additive to intrathecal bupivacaine and showed to have a significant prolonged duration of analgesia along with nausea and vomiting that were not statistically significant. Mahima gupta *et al.* also shown the duration of sensory blockade was 289.6 minutes in buprenorphine group and 493.6 minutes in dexmedetomidine group. In this study, 75 µg of buprenorphine was used instead of 60 µg to evaluate whether the increased dosage of 15 µg buprenorphine would help in further prolongation of duration of analgesia with a minimal side effects (PONV).

The mean onset of sensory block in buprenorphine group was 3.47 minutes whereas in dexmedetomidine group it was 2.57 minutes. It was not statistically significant. The mean onset of motor block in buprenorphine group was 3.83 minutes whereas in dexmedetomidine group, 4.13 minutes. It was not statistically significant. Duration of analgesia was taken from the time of intrathecal injection of drugs to the first supplementation of rescue analgesic when patient had VAS score of 4. In our study, the mean duration of analgesia was 332 minute. The prolongation of duration in our study could be explained by the dosage difference of buprenorphine (75 µg V/s 60µg). But the mean duration of analgesia in the studies conducted by Shaikh and Kiran *et al.* and Capogna *et al.* was 475 minutes and 430 minutes respectively which is very high than our study. This gross difference might be explained by the geriatric group of patients in Capogna *et al.* and lower limb surgeries included in Safiya *et al.* as noted by Mahima gupta *et al.*

Similar resuits were found in previous study by prakash Chandra *et al.*, compared intrathecal buprenorphine and dexmedetomedine with levobupivacaine for lower limb surgeries. The dexmedetomedine group had significantly prolonged duration of postoperative analgesia compared with buprenorphine similar to the results in our study. There was statistically no change in perioperative BP and HR Iin both the groups. Side effects like bradycardia and hypotension were not significant. The duration of analgesia in the dexmedetomidine group in the study conducted by Mahima gupta *et al.* was 493 minutes and the study conducted by Shah *et al.* was 474 minutes.

The duration of analgesia was significantly prolonged in the study done by Rajni Gupta *et al.* (478 minutes). In our study, the mean duration of analgesia was 502.13 minutes in dexmedetomidine group which was similar to above mentioned studies. Also, the study done by Eid *et al*. showed that duration of analgesia with dexmedetomidine Group was proportional to its dose.

In this study, Dexmedetomidine group had prolonged duration of analgesia compared to Buprenorphine group which was 51% higher than the later. Mahima Gupta *et al.* have shown similar results. The prolonged analgesic action of intrathecal α2 agonist is by decreasing the release of C-fibres neurotransmitters and by causing hyperpolarisation of neurons in the post synaptic dorsal horn.

The duration of motor block was taken from time of intrathecal drug administration to the time taken to attain modified bromage 3. The mean duration of motor block in Buprenorpine group was 298.6 minutes and in dexmedetomidine group was 432.33 minutes (p value 0.00).This was similar with the study conducted by Mahima gupta *et al.*, where the duration of motor block in dexmedetomidine group was 413.4 minutes and the study conducted by Rajni Gupta *et al.*, where the duration of motor block was 421 minutes.

The mean duration of motor block in buprenorphine group is 298.6 minutes, whereas the duration of motor block in Mahima gupta *et al.* study was 205.17 minutes which is significantly lower than our study. This could be explained by the increased dosage used in our study.

In our study itself, motor blockade in dexmedetomidine group was about 45% prolonged than Buprenorpine group. Such a prolongation of motor blockade may not be liked by many patients who have undergone surgeries that would end by one hour. In this perspective, Buprenorphine would be a better adjuvant. Also, the duration of 'pure' sensory blockade (after the wear of motor blockade effect) in dexmedetomidine group was twice that of buprenorphine group (70 v/s 34 minutes). Still, Dexmedetomidine is a better drug as it would spare the rescue analgesic requirements.

Conclusion

Our study concluded that the supplementation of Dexmedetomidine as an adjuvant to 0.5% levobupivacaine in spinal anesthesia produces longer duration of sensory and motor block but takes slightly more time to attain complete motor block as compared to Buprenorphine. Dexmedetomidine also provides an additional benefit of providing conscious sedation with fewer side effects. Both groups had stable and comparable hemodynamics.

References

1. G Edward Morgan, Jr MS. Mikhail, Michael J Murray. Clinical Anaesthesiology 2018,6.
2. Mohamed AA, Fares KM, Mohamed SA. Efficacy of intrathecally administered dexmedetomidine versus dexmedetomidine with fentanyl in patients undergoing major abdominal cancer surgery. Pain physician 2012;15:339-48.
3. Shaikh SI, kiran M. Intrathecal buprenorphine for post-operative analgesia; A prospective randomised double blind study. Journal of anaesthesia and clinical pharmacology 2010;26:35-8
4. Madhur Gupta, Neeru Goyal. Pain update 2005 Neurophysio- pharmacodynamics, Neuropathic and chronic pain and multimodal approach to pain management, Published by MSRMC and ISPRAT 2005;19-25.
5. Capogna G, Celleno D, Tagariello V, Loffreda-Mancinelli C. Intrathecal buprenorphine for postoperative analgesia in the elderly patient. Anaesthesia1988;43:128-30.
6. M Gupta, S Shailaja, K Sudhir Hegde. Journal of clinical and diagnostic research 2014;8(2):114-117.
7. Sapkal PS, Kulkarni KD, Rajurkar SS, Nandedkar pd. Comparative study of intrathecal clonidine and intrathecal Buprenorphine for postoperative analgesia after lower limb orthopaedic surgery. International Journal Current Res Rev 2013;5:87-91.
8. Prakash Chandra, Singariya Geeta, Kamal Manoj, Sethi Priyanka, Chauhan Singh Dilip, Khatri Chanda. Comparison of Dexmedetomidine or Buprenorphine as an Adjuvant to Levo Bupivacaine in Spinal Anaesthesia for Lower Limb Surgeries, Scholars Journal of Applied Medical sciences 2017;5(12c):4979-498.
9. Shah A, Patel I, Gandhi R. Haemodynamic effects of intrathecal dexmedetomidine added to ropivacaine intraoperatively and for postoperative analgesia. International journal of basic clinical pharmacology 2013:2:26-29.
10. Gupta R, Varma R, Bogra J, Kohli M, Raman R, Kushwala JK. A comparative study of intrathecal Dexmedetomidine and Fentanyl as adjuvants to Bupivacaine. Journal of Anaesthesiology and clinical Pharmacology July-september 2011,27(3).
11. Gupta R, Bogra J, Verma R, Kohli M, Kushwaha JK, Kumar S. Dexmedetomidine as an intrathecal adjuvant or postoperative analgesia. Indian journal of anaesthesia 2011;55:347-51.
12. Ding Z, Rafia RB. Identification of an additional supraspinal component to the analgesic mechanism of action of buprenorphine. British journal of pharmacology 2009;157:831-43.
13. Dixit S. Postoperative analgesia after caesarean section; an experience with intrathecal buprenorphine. Indian journal of anaesthesia 2007;51:515-8.
14. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alamedine MM, Al- yaman R *et al*. effect of low dose dexmedetomidine or clonidine on the characteristics of spinal block. Acta Anaesthesiol scand 2006;50:222-7.
15. Sunil Sharma. Pain update 2005 Neurophysio-pharmacodynamics, Neuropathic and chronic pain and multimodal approach to pain management, Published by MSRMC and ISPRAT 2005:71-81.
16. Soumya Samal, P. Rani, Chandrasekar LJ and Saubhagya kumar Jena. Intrathecal Buprenorphine or Intrathecal Dexmedetomidine for postoperative analgesia: A comparative study. The health Agenda, Online ISSN No:2320-3749.
17. Hala EA Eid *et al*. Studied dose related effect of intrathecal Dexmedetomidine with hyperbaric bupivacaine-a prospective randomized double blind study. Ain Shams Journal of Anesthesiology 2011;4(2);83-95.
18. FA Khan Gauhar. A Hamdani Comparision of intrathecal Fentanyl and Buprenorphine in urological cases Journal of Pakistan Medical Association 2006;56(6):277-281.
19. Leffler A, Frank G, Kishner K, Niedermirtl F, Koppert W, Reeh PW, Nau C. Local anesthetic-like inhibition of voltage-gated Na (+) channels by the partial μ-opioid receptor agonist buprenorphine. Anesthesiology 2012;116:1335-46.
20. Celik F, Gocmez C, Kamasak K, Tufek A Guzel A, Tokqoz O *et al*. The comparision of neuroprotective effects of intrathecal dexmedetomidine and metilprednisolone in spinal cord injury. International journal of surgery 2013;11:414-8.
21. Grewal A. Dexmedetomidine: New avenues, Journal of Anaesthesiology, Clinical Pharmacology 2011;27(3).