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Original Article

Anaesthesia Section

Comparative Study of Magnesium Sulphate versus Dexmedetomidine as an Adjuvant to Epidural Bupivacaine- A Randomised Controlled Trial

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ABSTRACT

Introduction: Neuraxial adjuvants are used to improve or extend analgesia. They have been utilised in several trials to prolong postoperative analgesia along with spinal anaesthesia, but as epidural anaesthesia is more haemodynamically stable, adding adjuvants to the above will have substantially less detrimental effects. Dexmedetomidine and magnesium sulphate may be used as adjuvants in neuraxial anaesthesia, along with local anaesthetics.

Aim: To determine the impact of adding magnesium and dexmedetomidine in the lower limb and lower abdominal procedures, as an adjuvant to epidural bupivacaine.

Materials and Methods: This randomised, single-blinded study was conducted on 90 ASA (American Society of Anaesthesiologists) class I and II patients in the Department of Anaesthesiology, Government Medical college, Kannur, Kerela from September 2015 to September 2016. Following randomisation using the lottery approach, the patients were divided into groups M, D, and C, and given the appropriate drugs through the epidural route. Group D: Bupivacaine 0.5% 10 mL+Dexmedetomidine 0.5 mcg/kg (in 1 mL 0.9% saline); group C: Bupivacaine 0.5% 10 mL+Saline 0.9% (1 mL); group M: Bupivacaine 0.5% 10 mL+$MgSO_4$ 50 mg (in 1 mL 0.9% saline). Monitoring was done for the onset, duration, haemodynamic parameters, level of motor and sensory block attained and any adverse outcomes. Data were collected, and statistical analysis was done by Statistical Package for Social Science (SPSS) version 17.0 and Analysis of Variance (ANOVA) with repeated measurements and the contingency coefficient test were both used.

Results: The mean age of group C, M and D was 58.4, 56.3 and 58.4 in years, respectively. D had greater postoperative analgesia (307.3±77.3 minutes), while the duration for the onset of sensory (13.1±1.3 minutes) and motor blockade was much shorter. Prolonged motor block and sedation, Ramsay sedation score >3 was observed in Group D.

Conclusion: The addition of dexmedetomidine to epidural bupivacaine may be beneficial, in the context of the prolonged duration of motor and sensory blockade and arousable sedation.

Keywords: Central neuraxial block, N-methyl-D-aspartate receptor agonist, Postoperative pain local anaesthetic

INTRODUCTION

Pain is an unpleasant sensation that originates from ongoing and impending tissue damage. Epidural placement is the safe, effective means of providing surgical anaesthesia and postoperative analgesia. No drug has yet been identified that specifically inhibits nociception without associated side effects.

Neuraxial adjuvants are used to improve or extend analgesia. These have been utilised to prolong postoperative analgesia along with spinal anaesthesia [1] but as epidural anaesthesia is more haemodynamically stable, adding adjuvants in the above will have a substantially less detrimental effect. Various drugs like dexmedetomidine, a selective alpha-2 adrenergic receptor agonist and magnesium sulphate may be used as an adjuvant in neuraxial anaesthesia along with local anaesthetics [1,2,3]. Regional anaesthesia also brings along with it the benefits of postoperative analgesia which is the most demanded benefit by patients. It can reduce or avoid the hazards and discomfort of general anaesthesia like sore throat, airway trauma and muscle pain. It also offers a number of advantages to outpatients undergoing surgery.

The most popular method for giving surgical patients anaesthesia as well as postoperative analgesia is epidural anaesthesia [4]. The most desirable characteristics of modern surgery include early postoperative movement, rehabilitation, and minimum pain and discomfort [5-7]. The gold standard medications include local anaesthetics like bupivacaine and lignocaine, either with or without adrenaline [7,8]. Traditional adjuvants include opioids like fentanyl, morphine, and buprenorphine; but they can have adverse effects including itching, urine retention, nausea, vomiting, and respiratory depression [9-11]. Alpha-2 agonists are one of many novel adjuvants to local anaesthetics that are currently being tested. These adjuvants have remarkable analgesic qualities and act by enhancement of the local anaesthetic, which is mediated by hyperpolarising nerve tissues by changing transmembrane potential and ion conductance at the locus coeruleus in the brainstem [12].

Another group of drug used as an adjuvant are magnesium sulphate. The analgesic effect of epidural Magnesium Sulphate ($MgSO_4$) is because of its non competitive antagonism of N-methyl-D-aspartate (NMDA) receptor [13]. Recent studies suggest the role of magnesium sulphate, as an adjuvant to local anaesthetics in spinal anaesthesia [14].

Noxious stimulation leads to the release of glutamate and aspartate neurotransmitters, which bind to the NMDA receptor. Activation of these receptors leads to calcium entry into the cell and initiates a series of central sensitisation and long-term potentiation in the spinal cord, in the response of cells to prolonged stimuli. NMDA receptor signaling, may be important in determining the duration of acute pain. Magnesium blocks calcium influx and non competitively antagonises NMDA receptor channels. Dexmedetomidine given epidural has more duration of sensory analgesia than magnesium sulphate in lower limb surgeries [15]. Recent studies done on

postoperative analgesia for Total Knee Replacement (TKR) [16] and thoracotomy [17] also has shown dexmedetomidine to be effective. They also mention that, magnesium can be given as an alternative.

Hence, the current study was conducted with an aim to compare the efficacy of Dexmedetomidine and Magnesium sulphate as an adjuvant to epidural bupivacaine. The primary objective was to compare the onset, duration of sensory and motor block. Secondary objective was to compare the side effects including hypotension bradycardia, nausea, and vomiting, sedation and shivering.

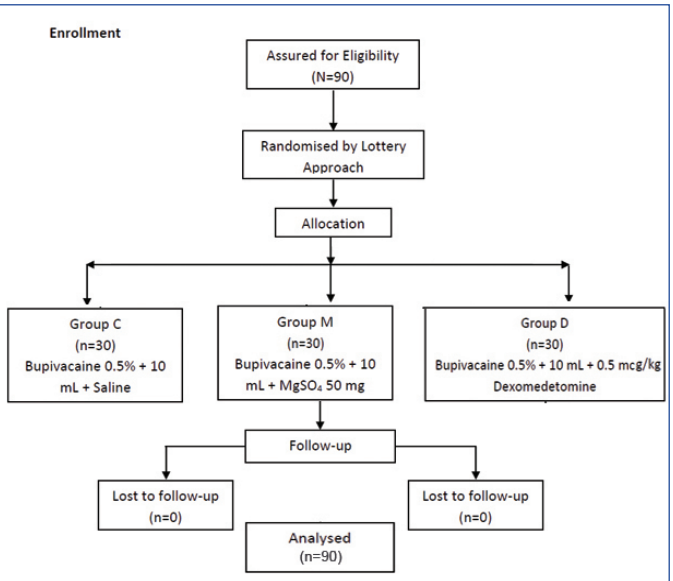
MATERIALS AND METHODS

This randomised single-blinded study was conducted in the Department of Anaesthesiology, Government Medical College, Kannur, Kerala, India, from September 2015 to September 2016. The Institutional Ethical Committee (G1.274712/ACME/2015) was obtained.

Inclusion criteria: All adults with age 20-80 years, ASA I and II patients scheduled for lower limb and abdominal surgeries were included in the study.

Exclusion criteria: Patients with a history of adverse reactions to any study medications, history of analgesic use and chronic pain syndrome, patients with communication difficulties, age >80 years, infection at the injection site, mental disturbances, coagulopathy, cardiac complications were excluded.

Sample size calculation: The sample size was determined using data from the study by Shahi V et al., [15]. The mean time to first epidural top up and difference in mean value of first epidural top up between group D and group M is (587.8±64.3 min) and (226.3±60.9 min) respectively. Therefore, with 80% power and a level of significance of 5%, 90 patients (30 in each group) were adequate to identify a difference of 25% across groups [Table/Fig-1].



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) chart.

Procedure

Soon after hospital admission, a full preoperative clinical assessment was performed. Complete blood count, random blood sugar, renal function test, serum electrolytes, screening tests, Electrocardiograms (ECG), and chest X-ray were done preoperatively. Following randomisation using the lottery approach, 90 patients who underwent lower limb and lower abdominal surgery were selected based on the criteria and randomly assigned to three groups- M, D and C, 30 patient each. They are as follows-

- Group C: Bupivacaine 0.5% 10 mL+Saline 0.9%;
- Group M: Bupivacaine 0.5% 10 mL +$MgSO_4$ 50 mg (in 1 mL 0.9% saline); (1 mL).
- Group D: Bupivacaine 0.5% 10 mL+Dexmedetomidine 0.5 mcg/kg (in 1 mL 0.9% saline);

Following a thorough preanaesthesia evaluation and obtaining written consent, the patient was informed of the procedures and any potential complications. The night before surgery, all study participants received an injection of ranitidine 50 mg i.v. and a 0.5 mg alprazolam tablet as premedication. Before surgery, they were kept off solid food for atleast six hours and clear liquids for two hours.

Following a patient centred explanation of the operation, signed informed consent was obtained. An 18-Gauge i.v. cannula was placed under local anaesthetic infiltration, as soon as, the patient entered the operating room, and an infusion of Ringer's lactate 20 mL/kg preloading was commenced. The patients were hooked up to a multiparameter monitor that recorded oxygen saturation, heart rate, non invasive assessments of blood pressure, mean arterial pressure, and continuous ECG. Both the heart rate and the average systolic blood pressure were noted. A continuous visual ECG from lead II was used to assess the heart rate and rhythm.

The L2-3 or L3-4 epidural space was identified by the loss of resistance technique with an 18 G Tuohy needle under aseptic conditions after local anaesthetic infiltration of the skin. A multi-orifice catheter was placed up to 4 cm in the epidural space. A test dose of 3 mL of epidural lignocaine 2% with adrenaline confirmed the epidural catheter's proper insertion (1:200,000). Epidural medication was administered following proper epidural catheter insertion. Time to reach the highest dermatomal level, time to reach T10 sensory level, mean pulse rate and mean arterial pressure were recorded at the time of drug delivery, at 5 min intervals for the first 20 min, then 10 min and 15 min intervals upto 60 minute, regression from Bromage level 3, need for a first epidural top-up, and perioperative complications like bradycardia, hypotension, nausea, vomiting, shivering, and sedation based on Ramsay sedation score were all factors that were evaluated. Patients were monitored for any delayed problems, for 72 hours.

STATISTICAL ANALYSIS

Data were collected, and statistical analysis was done by SPSS version 17.0, and presented as tables, figures, graphs, and diagrams. An independent samples t-test was employed to compare the means for the two groups. ANOVA with repeated measurements and the contingency coefficient test were both used. All information was displayed as mean±SD (Standard Deviation). The student's t-test was used to assess the demographic data. Results were shown in table and figure as numbers and percentages for each parameter for discrete data and as an average (mean±SD) for continuous data. The statistically significant difference in the parameters measured between the study groups was determined using the Student's t-test. A p-value of less than 0.05 was considered statistically significant in all the tests, mentioned above.

RESULTS

Between the three groups, there were no significant statistical variations in terms of gender, height, or weight [Table/Fig-2]. Most of the patients were over the age of 40 years; 43.3% of patients

Demographic variables	Group C	Group M	Group D	p-value
ASA				
I	13	14	15	0.89
II	17	16	15	
Age (years, Mean±SD)	58.4±16.1	56.3±14.5	58.4±14.7	0.827
Gender n (%)				
Male	9 (30)	17 (56.7)	17 (56.7)	0.079
Female	21 (70)	13 (43.3)	13 (43.3)	
Mean BMI (kg/m^2)	22.75±1.81	22.96±1.63	22.31±1.76	0.91

[Table/Fig-2]: Comparison of demographic variables.
ASA: American society of anaesthesiologist; BMI: Body mass index

in group M and 56.7% in groups C and D had no concomitant diseases [Table/Fig-3].

Co-existing diseases	Group C n (%)	Group M n (%)	Group D n (%)	p-value
Diabetes mellitus	9 (30)	5 (16.7)	6 (20)	0.726
Hypertension	8 (26.7)	7 (23.3)	9 (30)	
Bronchial asthma	0	1 (3.3)	1 (3.3)	
COPD	0	1 (3.3)	1 (3.3)	
Nil	13 (43.3)	17 (56.7)	13 (43.3)	

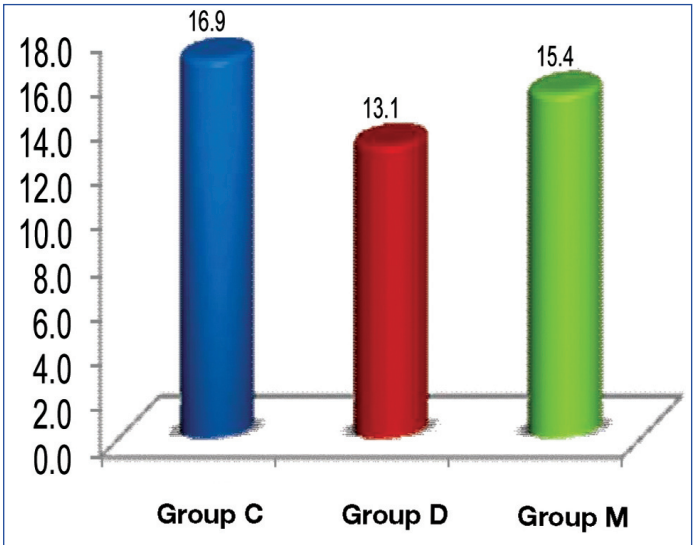
[Table/Fig-3]: Comparison of co-existing disease based on groups.
COPD: Chronic obstructive pulmonary disease

For groups C, D, and M, respectively, the times required to reach the sensory block to the T10 level were 16.9±1.2, 13.1±1.3, and 15.4±1.3 min, respectively. The time for onset of sensory block in group D was considerably shorter than that of the other two groups. In all three groups, the maximum dermatomal level obtained was comparable [Table/Fig-4].

Observed variables	Group C	Group M	Group D	p-value
Time to reach sensory block T10 in minutes (mean±SD)	16.9±1.2	15.4±1.3	13.1±1.3	<0.001
Maximum sensory dermatomal level T6 N (%)	17 (56.7)	20 (66.7)	17 (56.7)	0.638
1st epidural top-up in min (mean±SD)	144.2±22.4	195.9±33.1	307.3±77.3	<0.001
Regression from Bromage 3 in min (mean±SD)	102.6±16.3	149.9±25.1	228.0±49.8	<0.001

[Table/Fig-4]: Time (minutes) to achieve various landmarks.
p-value <0.001- statistically highly significant

The duration between the initial epidural bolus to the first epidural top-up was the longest (307.3±77.3 min) in the group D and then the group M (195.9±33.1 min) and the shortest (144.2±22.4 min) in the group C of patients. The differences among groups were highly significant (p-value <0.001) [Table/Fig-5].

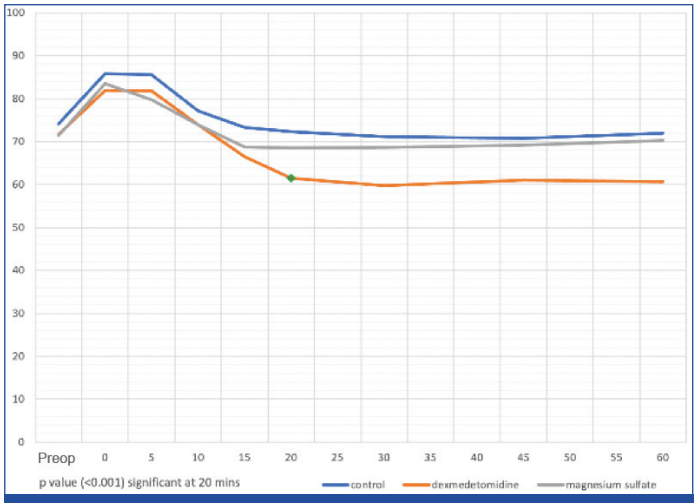


[Table/Fig-5]: Comparison of time to reach sensory block T10 min based on group.

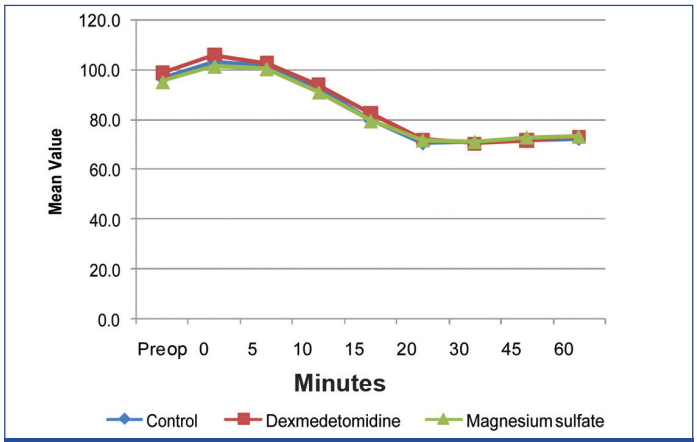
The group D experienced the longest time for regression from Modified Bromage level 3 (228.0±49.8 min), followed by the group M (149.9±25.1 min), and the group C (102.6±16.3 min) [Table/Fig-4].

When the patient's pulse rates were taken, there was a statistically significant difference between the three groups' mean pulse rates (p-value <0.001). After 20 minutes the medication was administered, the mean pulse rate in group D decreased [Table/Fig-6].

The patient's Mean Arterial Pressure (MAP) was monitored at multiple time intervals [Table/Fig-7], and there was no statistically significant difference (p-value >0.05) in the MAPs of the three groups [Table/Fig-8].



[Table/Fig-6]: Comparison of pulse rate at different time intervals.



[Table/Fig-7]: Comparison of MAP at different time intervals.

Haemodynamic variables (Mean±SD)	Group C	Group M	Group D	p-value
Pulse rate at 30 min	71.1±6.4	68.6±5.5	59.7±4.6	<0.001
MAP at 30 min	71±4.8	71.2±5.6	70.5±6	0.868

[Table/Fig-8]: Comparison of haemodynamic variables.
MAP: Mean arterial pressure; p-value <0.001 was statistically highly significant

During and after surgery, adverse effects such as hypotension, bradycardia, nausea, vomiting, sedation, and shivering were observed. The group D experienced statistically significant bradycardia episodes. In all three groups, hypotension, nausea, and vomiting were comparable. The group receiving dexmedetomidine had a higher sedation score and was graded, as per Ramsay sedation score. The prevalence of shivering was more in the control group [Table/Fig-9].

Side effects	Group C n (%)	Group M n (%)	Group D n (%)	p-value
Bradycardia	3 (10.0)	4 (13.3)	18 (60.0)	<0.001
Nausea and vomiting	1 (3.3)	0	0	0.364
Ramsay sedation score	2 (6.7)	3 (10.0)	26 (86.7)	<0.001
Shivering	9 (30.0)	2 (6.7)	0	0.001

[Table/Fig-9]: Side effects.
p-value <0.001- statistically highly significant

DISCUSSION

The epidural local anaesthetic injection is a common and effective method of anaesthesia and postoperative analgesia for abdominal and lower limb procedures. To prevent monopharmacy related adverse effects and to improve the quality of anaesthesia and postoperative analgesia, a variety of pharmacological substances are utilised as adjuvants to local anaesthetic drugs.

The effects of the addition of dexmedetomidine vs magnesium sulphate to epidural bupivacaine were compared for sedation,

onset and duration of motor and sensory block, maximum sensory block, analgesic efficacy in the perioperative period, haemodynamic variables, and side effects along with a control group. It was found that, dexmedetomidine be a better agent in prolonging the motor and sensory block intraoperatively and the duration of effective postoperative analgesia with good arousable sedation. Neuraxial adjuvants are used to improve the quality, lengthen the duration, and accelerate the neural blockade's onset (lower latency). Examples include opioids, vasoconstrictors, alpha-2 adrenoreceptor agonists, cholinergic agonists, NMDA antagonists, and Gamma-aminobutyric acid (GABA) receptor agonists. It produces analgesia by hyperpolarising, which prevents the release of C-fiber transmitters and postsynaptic horn neurons. Adjuvant properties of magnesium sulphate have been mentioned in recent study research in combination with a local anaesthetic. It blocks NMDA channels in a voltage-dependent way and produces a reduction of NMDA-induced currents [18].

Most of the patient population was above 40 years of age with a higher incidence of the orthopaedic lower limb and gynaecological surgeries in those above 40 years.The time taken for the sensory level to reach the T10 block was significantly lower with group D compared to the other two groups. Similar findings were seen in the study by Shahi V et al., magnesium sulphate and dexmedetomidine were used as an adjuvant with the epidural [15].

Compared to the control and magnesium group, 0.5 mcg/kg of dexmedetomidine when used as an additive to epidural bupivacaine prolonged the duration of sensory blockage, so the time taken for the first epidural top-up was significant. The dexmedetomidine group had the longest interval followed by the magnesium group while the control group of patients had the shortest interval. Zhang X et al., did a systematic review and meta-analysis of 12 randomised controlled trials and found that epidural dexmedetomidine administration prolonged the duration of analgesia [19]. The study by Kaur S et al., showed that, 1 mcg/kg dexmedetomidine along with 0.75% ropivacaine, prolonged sensory analgesia with a time duration of (496.56±16.086 min while in the present study it was 307.3±77.3 min probably as the dose taken was 0.5 mcg/kg dexmedetomidine [20]. Comparable values were found in the study done by Karhade SS et al., [1]. The rescue analgesia requirement was proven to be less which is supported by Elhakim M et al., where in one lung ventilation for thoracic surgeries epidural dexmedetomidine was used and found that the requirement of paracetamol was minimal [21]. The analgesic sparing effect has been proven in several studies [17].

The motor blockade was assessed by the Modified Bromage scale. Dexmedetomidine has a visible edge over magnesium sulphate, as it enables the establishment of prolonged motor block. The time for regression from modified Bromage level 3 was longest in the group D followed by the group M and shortest in the group C. It correlates with the study by Gupta K et al., where motor blocks were more pronounced in the dexmedetomidine group with 25 mcg given epidurally along with 0.5% levo bupivacaine [22]. The delayed recovery of motor function proves to be a disadvantage for its use in daycare surgeries this was supported Shahi V et al., [15] where prolongation of motor block was observed. The prolongation of motor block may be due to the binding of alpha-2 adrenoreceptor agonist to the motor neuron of the dorsal horn [23,24].

In the present study, heart rate and mean arterial pressure were recorded. A mean pulse rate of 59.7 at 20 minutes was observed in the group D, but it did not require any intervention in the intraoperative period, hence, it was clinically insignificant. This is in accordance with a meta-analysis conducted in 2021 by Li N et al., [25], where maternal bradycardia was observed in the eight randomised control trials studied. It was found that, there was no foetal compromise and hence, no intervention was required. Maternal bradycardia was observed from 15 mins to 2 hour time period when dexmedetomidine was given in a fixed range of 50 mcg to all patients by Afandy ME et al., who conducted a study to see the effect of dexmedetomidine, when administered in labour analgesia [26].

Group D had the highest sedation score compared to the other two groups but patients showed arousable sedation. It was assessed by sedation scale used in study conducted by Bajwa SJ et al., [27]. Hence, occurrence of respiratory depression was minimal. Shivering was observed more in the group C, than the other two groups as known dexmedetomidine inhibits neuroendocrine and haemodynamic response at the central and spinal levels. Magnesium also decreases shivering, but the mechanism is still under research. The most probable mechanism being after administration of epidural, the vasoconstriction developed is counteracted by the vasodilatory property of magnesium [28,29].

Limitation(s)

ASA I and II patients were included and hence, the effect of dexmedetomidine in elderly with severe cardiovascular co-morbidity, has yet to be studied. Magnesium was used on a fixed dose and dose variability and the impact was not studied.

CONCLUSION(S)

To conclude, 0.5 mcg/kg of dexmedetomidine added to epidural bupivacaine has shown to be a better agent in prolonging the motor and sensory block, intraoperatively. It also prolonged the the duration of effective postoperative analgesia with good arousable sedation and clinically insignificant bradycardia, as side effects compared to magnesium sulphate.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
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- Manual Googling: Dec 03, 2022
- iThenticate Software: Dec 20, 2022 (20%)

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- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

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