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Original Research Article

Block characteristics of different doses of intrathecal dexmedetomidine when combined with low dose heavy bupivacaine for gynecological surgeries: a double blind, randomised comparative study

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Abstract: Intrathecal dexmedetomidine is being explored as a new adjunct to bupivacaine for neuraxial anesthesia. Objective is to study variability in various parameters of sensory and motor blockade using different doses of dexmedetomidine intrathecally while reducing the dose of heavy bupivacaine in gynecological surgeries. A unicenter, parallel, double blind randomized prospective controlled trial. 75 females undergoing gynecological procedures, fulfilling the inclusion/exclusion criteria received a total volume of 2.5 ml drug intrathecally, accordingly: D1 (n=25) - hyperbaric bupivacaine 7.5 mg (1.5ml) with 5 µg (1ml) dexmedetomidine. D2 (n=25) - hyperbaric bupivacaine 7.5 mg (1.5ml) with 7.5 µg (1ml)dexmedetomidine. D3 (n=25) - hyperbaric bupivacaine 7.5 mg (1.5ml) with 10 µg (1ml) dexmedetomidine. The outcomes of the study were planned before data collection began. Statistically (p=0.005), onset of T10 level sensory block was dose dependant, fastest in D3 (2.36±0.81 min) and slowest in D1 (3.12±0.83 min) and so was the onset of motor block (p<0.001), time in D3 (2.32±0.63 min) and in D1 (3.56±0.96 min). In peak level, two segment regression time and total time of sensory block, there was no intergroup difference. Dexmedetomidine did effect the total time of motor block, but not in dose dependent pattern (p=0.037). With neurexial dexmedetomidine , onset of sensory and motor block is faster with increasing the dose. Total volume of bupivacaine can be reduced to significant levels to achieve a higher peak level, prolonged two segment regression time and total time of sensory and motor block.
Keywords: Neuraxial, bupivacaine, dexmedetomidine, alpha 2 agonist, adjuncts.

INTRODUCTION

Neuraxial anesthesia has enjoyed an acknowledging and lucrative history since the late nineteenth century [1], after the discovery of local anesthetic and is currently more popular and accepted than ever. Gynecological surgeries like abdominal and vaginal hysterectomies are often done under regional anesthesia due to certain advantages over general anesthesia [2] and eventually avoiding general anesthesia and its complications [3].

Although now-a-days low dose, heavy (hyperbaric) bupivacaine is being used for adequate spinal anesthesia abating the chances of neuro and cardio toxicity encountered with other local anesthetics when used in spinal anesthesia [4]. Spinal anesthesia requires strict dose calculations as the drugs are directly injected in the intrathecal space. The side effects like hypotension, vomiting, respiratory depression are frequently encountered and total spinal block though rare are all directly dose related [5]. Reducing the dose of local anesthetic to prevent the above said side effects are not feasible beyond a certain point as then visceral pain is unbearable for the patient and it is unethical for the anesthesiologist. Above mentioned factors provided us with the impetus to add adjuncts with local anesthetics for intrathecal use.

Different adjuvants have been used to supplement intrathecal local anesthetics with the possible advantages of improving and enhancing the quality and duration of anesthesia, reducing the dose of local anesthetics and their side effects, delaying the onset of postoperative pain and reducing postoperative

analgesic requirements. Most common adjunct areopioids which offer the above described advantages [6]. However, side effects such as potentially catastrophic delayed respiratory depression, nausea, vomiting, pruritus, constipation and urinary retention [7] have prompted further research to develop non opioid analgesics with less worrisome side effects.

Since first reports of clonidine, an α2adrenoceptor agonist, the indications have continued to expand with clonidine as its prototype [8].

In December 1999, dexmedetomidine, a more potent α2 agonist was approved by FDA for clinical practice as a short-term sedative. In addition, dexmedetomidine is shorter acting drug than clonidine and has a reversal drug for its sedative effect; atipamezole[9].These properties render dexmedetomidine suitable for sedation and analgesia during the whole perioperative period.Furthermore, their role in pain management and regional anesthesia is expanding.

The use and studies of intrathecal dexmedetomidine with low dose bupivacaine has been sparse in the past. We therefore carried out an intergroup study on the basis of the similar hypothesis of using dexmedetomidine as an adjunct for neuraxial blocks with the following objectives:

OBJECTIVES

- To study and compare the characteristics of the sensory and motor block when using different doses of dexmedetomidine with low dose bupivacaine.
- To find the optimal dose of dexmedetomidine as an adjunct using primary outcome of the study as time for the sensory block to reach the T10 level.

METHOD

After approval by institutional ethical committee this unicenter, parallel, double blind randomized controlled trial with allocation ratio of 1:1:1 was carried out at Dr.R.P.G.M.C.,Kangra at Tanda (H.P.) in females undergoing gynecological procedure, fulfilling the inclusion exclusion criteria.

Inclusion criteria

1. Females
2. Age group 30- 70 years
3. ASA class I-III
4. BMI 18.5- 39.9
5. Undergoing gynecological surgery

Exclusion criteria

1. Patient's refusal for the block
2. Uncontrolled and labile hypertension
3. Patients using α2-adrenergic receptors antagonists
4. Patients noted to have dysrhythmias on the electrocardiogram (ECG)
5. Allergic to study drugs
6. Absolute contraindication for spinal anesthesia
7. BMI > 40

The anesthetic procedure was explained to the patients enrolled for study and thereafter written informed consent was taken.

As being double blinded controlled trial, the patients were allocated to one of the three groups by randomization with the help of computer generated random numbers.

All patients were kept nil orally for at least eight hours before the procedure. They were given premedication in the form of tablet alprazolam 0.5 mg and tab ranitidine 150 mg at 6 am on the day of surgery. On arrival to operation theatre standard monitoring of ECG, NIBP and pulse oximetry was started and a peripheral i.v. line was started by 18G cannula on the nondependent arm. The patients were preloaded with ringer lactate at the rate of 10 ml/kg/hour. After proper positioning of the patient a spinal puncture was performed by a blinded anesthesiologist. The procedure was done under all aseptic conditions, in right lateral position, with a 26 G quincke needle, in L3- L4 space.

All patients received 2.5 ml of drug intrathecally after checking the free flow of CSF according to these 3 groups by the blinded anesthesiologist:

Group D1- patients received intrathecal 0.5% hyperbaric bupivacaine 7.5 mg (1.5ml) with 5 µg (1ml) dexmedetomidine (preservative free) diluted in normal saline.

Group D2-patients received intrathecal 0.5% hyperbaric bupivacaine 7.5 mg (1.5ml) with 7.5 µg (1ml) dexmedetomidine (preservative free) diluted in normal saline.

Group D3- patients received intrathecal 0.5% hyperbaric bupivacaine 7.5 mg (1.5ml) with 10 µg (1ml) dexmedetomidine (preservative free) diluted in normal saline.

Drug solutions were prepared by an anesthesiologist not involved in the study.

We evaluated the block characteristics under the following headings:

1. Peak level - highest level of dermatome block.
2. Time for the sensory block to reach the T10 level
3. Total duration of sensory block - was taken as the total time till regression of sensory block to a dermatomal level of S_1.
4. Total duration of motor block – time taken to achieve bromage score 0.
5. Time for two segment regression of sensory block - time interval between peak sensory blockade and reappearance of pinprick response at two segments lower than the peak level.

Onset of sensory block - defined as interval between the end of intrathecal injection and onset of sensory blockade and was demonstrated as loss of sensation to pinprick.

Onset motor block - the interval between the end of injecting the drug intrathecally and complete motor paralysis (bromage 3)

We evaluated the intra and inter group differences in the above said parameters.

For assessment of sensory loss pin prick test was followed using a blunt 25 G needle along the mid-clavicular line bilaterally at 3, 6, 9, 12, 15, 20, 25 and 30 min, and then every 15 min thereafter. The motor level of block was assessed according to modified bromage scale [10] to know the time to reach maximum bromage level and the time to regression of motor block to bromage 0.

Modified Bromage scale:

0 the patient is able to move the hip, knee and ankle.
1 the patient is unable to move the hip, but is able to move the knee and ankle.
2 the patient is unable to move the hip and knee, but is able to move the ankle.
3 the patient is unable to move the hip, knee and ankle.

All patients were administered oxygen through Hudson mask at the rate of 5 liters per minute and they were monitored intra operatively for systolic, diastolic, mean blood pressure, heart rate, oxygen saturation, respiratory rate and level of sedation every 1 minute for first 10 minute, then every 5 min for half an hour and then every 15 minute till the end of surgery in operating room and also in recovery room.

Any hypotensive (SBP< 70 mmHg) episode was treated with injection ephedrine 6 mg bolus and the episodes of bradycardia (HR< 40 beats/min) were treated with intravenous atropine 0.02 mg/kg.

The surgery was allowed to start after the attainment of T10 level of sensory block.

Before starting the study, ethical clearance was taken from the institutional ethical committee. Keeping in view the following I.C.M.R guidelines and Helsinki declaration the consent form was obtained from all the patients before they were shifted to O.T.

SAMPLE SIZE:

Computed using t test to compare means of time for the sensory block to reach T10 level between the groups. For 0.8 per SD with 95% confidence level and 80% power we require 25 evaluable patients in each group. We enrolled total of 83 patients who were randomly allocated to 1 of the 3 arms of the study and 75 were analyzed.

RANDOMISATION:

block randomization with variable block size was carried out to allocate enrolled patients in to 1 of the 3 groups and this was done by using computer generated numbers which were kept in sealed opaque envelops by a non participating statistician.

BLINDING:

Patient and the principal investigator were both blinded in the study.
The drug was diluted to its specific dilution by a non participating anesthesiologist and 1ml of it was added to the heavy bupivacaine prior to its administration in neuraxial space without disclosing the dilution to the principal investigator.

STATISTICAL TOOLS

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software.

The values were represented in Number (%) and Mean± SD.

Continuous covariates were compared using analysis of variance (ANOVA). The comparisons were studied using Chi-square tests, Fisher's test or student "t"/ Independent sample "t" test.

Level of significance: "p" <0.05 was considered statistically significant.

RESULT

The present study was carried out with 75 female patients at Dr. Rajendra Prasad Government Medical College, Kangra, Tanda (H.P.) over a period of 18 months.

DEMOGRAPHY (table1)

Mean age of patients was 47.44±9.69 years in Group D1, 44.80±8.53 in Group D2 and 45.68 ± 8.98 years in group D3.

Mean BMI of patients in group D1 had a mean value of 20.90±2.44 kg/m^2, 20.93±2.51 kg/m^2 in group D2 and 20.57±2.09 kg/m^2 group D3.

Majority of cases, *i.e.* 20 (80%) patients each, in groups D1 and D2 were ASA grade I, while remaining 5 patients (20%) each were ASA grade II. 18 (72%) patients in group D3 were ASA grade I and 7 patients (28%) were ASA grade II.

Mean duration of surgery was 85.80±26.40 minutes in group D1, 92.20±19.04 minutes in Group D2 and 84.00±19.63minutes in group D3. On comparing the data statistically, no significant difference among the groups was observed with respect to mean age, BMI, duration of surgery and ASA grade (p>0.05).

Primary outcome: time till T10 sensory block

BLOCK CHARACTERISTICS (table 2)

PEAK LEVEL OF SENSORY BLOCK

In group D1, median value for peak level of sensory block was T6 whereas in groups D2 and D3 it was T4. Though groups D2 and D3 achieved a higher level of sensory block yet **the association was not significant statistically** (p=0.206).

TIME TAKEN TO ACHIEVE T_{10} LEVEL OF SENSORY BLOCK

Optimum sensory block in order to start the surgery, taken as sensory block at T_{10} level, was achieved fastest in group D3 (2.36±0.81 min) and maximum time was taken in group D1 (3.12±0.83 min) to achieve T_{10} level as shown in fig 1. Mean time taken to achieve T_{10} level sensory block was 2.44±0.96 min in group D2. **Statistically, there was a significant difference in the three groups (p=0.005).**

MOTOR BLOCK

- TIME TAKEN TO ACHIEVE BROMAGE 3

Mean time taken to achieve adequate motor block (Bromage score 3) was minimum in group D3 (2.32±0.63 min) and maximum in group D1 (3.56±0.96 min), illustrated in fig 1. Mean time taken to achieve optimum motor block was 3.20±1.04 min in group D2. **Statistically, there was a significant difference between the three groups (p<0.001).**

- TIME TAKEN TO ACHIEVE BROMAGE 0

Mean time taken to achieve bromage 0 was minimum in group D2 (205.52±45.42 min) and maximum in group D3 (246.56±59.63 min). In group D1, this time was 233.80±62.67 min. **Statistically, there was a significant difference among the groups (p=0.037).**

REGRESSION OF SENSORY BLOCK BY TWO SEGMENT

In group D1, mean time taken for regression of sensory block by two segment was 148.44±38.17 min. In group D2, regression of sensory block by two segment was earliest with a mean value of 132.20±31.36 min and in group D3 regression of sensory block by two segment was observed at a mean value of 148.60±32.55 min. Statistically, there were no significant differences among the three groups (p=0.157).

TOTAL DURATION OF SENSORY BLOCK

. Total duration of sensory block was maximum in group D2 (390.28±61.09 min) and minimum in group D1 (363.60±91.22 min). In group D3, this duration was 381.60±79.26 min. statistically, the difference among groups was not significant (p=0.473).

DISCUSSION

To summarize our study:

1. The onset of sensory blockade to reach T10 dermatome was fastest when 10 µg dexmedetomidine was used intrathecally and hence concluded to be dose dependent.
2. The onset of motor blockade was also dose dependent and was fastest in 10 µg dexmedetomidine group.
3. The time for 2 segment regression of the sensory block was higher with 10 µg dexmedetomidine but the study revealed that there was no statistical intergroup difference.
4. The peak level of sensory block, prolongation in the total time of sensory block and motor

block were not related to the dose of dexmedetomidine used intrathecally.

Depending on a number of variables and factors the duration of the subarachnoid block is liable to vary and it provides an unpredictable duration of anesthesia for surgery and may require supplementation in the form of epidural block (more time consuming, cumbersome and costlier) [11] or general anesthesia.

Addition of adjuncts is not new to the world of anesthesia. Studies found as early as 1892 have shown the use of bicarbonate, to increase the pH of the local anesthetic and augmenting its potency[12].Various drugs and their effect as adjuncts like vasoconstrictors[13], opioids[14], neostigmine [15], ketamine [16], midazolam [17] etc. have been studied over years. α2adrenoceptors, clonidine has an established role in neuraxial anesthesia [8].Dexmedetomidine, a rather intense and highly selective α2adrenoceptor agonist [18], emerges as an approaching adjunct with a number of studies elaborating the list of benefits and evident side effects [19] of this drug when used with local anesthetics.

In a study conducted by Vincent W. S. Chan et al, "Determining minimum effective anesthetic concentration of hyperbaric bupivacaine for spinal anesthesia", in 2000 [20], it was concluded that 7.5mg of heavy bupivacaine when given in subarachnoid space failed to provide complete anesthesia consistently, even in the presence of 0.75% concentration of the drug.

In our study we have used 7.5 mg of 0.5% hyperbaric bupivacaine intrathecally with different doses of dexmedetomidine (5, 7.5 and 10μg respectively) as adjunct and achieved a satisfactory and comfortable level of block in order to successfully complete the surgeries.

Although, the exact mechanisms of dexmedetomidine in prolongation of subarachnoid block is still being speculated, the most probable mechanism is the presence of massive number of α2-adrenoceptor in the substantial gelatinosa of the spinal cord, which hyperpolarize the nociceptive neurons stimulated by the A and C nociceptive fibers. It also reduces the release of substance P and glutamate, essential for nociception and its transmission. Other actions are suppressing the release of noradrenaline via α2-adrenoceptor (locus coeruleus), known to be an important modulator of nociceptive neurotransmission [21].The lack of significant side effect like respiratory depression, itching, constipation makes dexmedetomidine an attractive choice as an adjuvant for subarachnoid block.

The intriguing question arising is, what is the appropriate dose of dexmedetomidine, to be used in subarachnoid block. Various animal studies have shown a wide range of dose of dexmedetomidine used without significant adverse effects but a meta-analysis published in the BJA, 2013 on effects of per neural dexmedetomidine [19]has shown that dose >6μg/kg is implicated with demyelination of the nerves in rabbits when injected via epidural route. In the present study, keeping in mind the doses of dexmedetomidine used in various previous studies, it was decided to use a total dose of 5μg, 7.5 μg& 10 μg which is ≤ 0.2μg/ kg.

BLOCK CHARACTERISTICS (TABLE 2)

Peak sensory level of block: In our study it was established that the peak level of sensory block was much higher as compared to the use of 7.5mg 0.5% bupivacaine without any adjunct [11].

In group D1, median value for peak level of sensory block was T6 whereas in groups D2 and D3 it was T4. Though groups D2 and D3 achieved a higher level of sensory block yet the association was not significant statistically (p=0.206).

In our study the total volume of drug given in the subarachnoid block was 2.5 ml and it was 2.5ml and 3ml in the study by Al-Ghanem [22] et al. and Rajni Gupta et al. [23] respectively. The peak levels achieved in their studies were also comparable with our study.

Onset time of sensory block to reach T_{10}dematome (figure 1). Our study revealed, mean time taken to achieve T_{10} sensory block was minimum in group D3 (2.36±0.81 min) and maximum in group D1 (3.12±0.83 min) statistically, there was a significant intergroup difference (p=0.005). It was concluded that the time required to reach T_{10} sensory level block was inversely related to the dose of dexmedetomidine used intrathecally.

Onset of motor block (figure1): In our study we found that the mean time taken to achieve optimum motor block (bromage score 3) was minimum in group D3 (2.32±0.63 min) and maximum in group D1 (3.56±0.96 min) and 3.20±1.04 min in group D2. Statistically, the three groups showed significant difference in the mean time taken to reach bromage score 3 in a dose dependent fashion (p<0.001).

To support our study, various other studies also showed a dose dependent pattern in the onset of sensory block but the time for sensory block to reach T_{10} was comparatively quicker in our study in all the three groups when compared to the studies by Al-Ghanem, Rajni Gupta and Hala E A Eid [24].

These results were comparable with the studies conducted by Al-Mustafa MM et al [25], in which they compared a dose of 5 µg and 10 µg dexmedetomidine with saline in combination with 12.5 mg intrathecal hyperbaric bupivacaine. In their study the mean time to reach bromage 3 differed from ours but dose dependent fashion of motor block was concluded.

Time taken for two segment regression of sensory block (figure 2):

In our study we found that the time taken for regression of the sensory block by two segment was increased with the use of dexmedetomidine as an adjunct. In Group D2, two segment regression of sensory block was earliest with a mean value of 132.20±31.36 min. In Group D3 it was delayed, with a mean value of 148.60±32.55 min. statistically, there were no significant differences among the groups (p=0.157). Hence concluding that regression time for two segment was not directly related to the dose of intrathecal dexmedetomidine.

Our results were equivalent when compared to the study conducted by Rajni Gupta[23] et al, "A comparative study of intrathecal dexmedetomidine and fentanyl as adjuncts to bupivacaine.

Time taken for regression of motor block to reach bromage 0 (figure 2):

Our study revealed that motor block was intensely prolonged when dexmedetomidine was added. Statistically, there was a significant difference among the groups (p=0.037) but the increase in duration of motor block was not dose dependant.

Motor block prolongation by α2 adrenoreceptor agonists may result from binding of these agonists to motor neurons in the dorsal horn of the spinal cord.

The study by Hala E A eid et al [24] so concludes that dexmedetomidine intrathecally prolongs the motor block, but revealed that the total time of motor block is a dose dependent. On comparison with the study by Rajni Gupta, the total time of motor block is comparatively lesser in our study. The total time of motor block is 421 ± 21mins in their dexmedetomidine 5µg group whereas in our study it was 233.80 ± 62.67 min in D1 group. The difference can be attributed to the higher dose and volume of bupivacaine used in their study.

Total time of sensory block (regression to S_1) (figure 2):

it was minimum in group D1 (363.60±91.22 min) and maximum in group D2 (390.28±61.09 min). In our study there was no intergroup statistical difference in the total duration of sensory block, although the time for sensory block is prolonged as supported by a number of studies. In a meta analysis of dexmedetomidine [19] published in 2013, there was an increase in the total duration of sensory block by 72% when compared to the use of local anesthetic alone.

CONCLUSIONS

Dexmedetomidine seems to be anattractive adjunct to low dose intrathecal bupivacaine for gynecological surgeries. Benefits of 10ug dexmedetomidine as adjuncts outweighed those of 5ug dexmedetomidine group from surgical view point. The onset of sensory and motor block was much faster as compared to the other groups.

The time for 2 segment regression and total time of sensory block was not significantly different in the 3 groups. Total time to reach bromage 0 was prolonged in 10ug dexmedetomidine which has no additional benefits rather is not desired.

Hence in conclusion if onset of sensory and motor block is not the deciding factor 5ug dexmedetomidine with 7.5mg bupivacaine provides optimal and suitable block conditions for gynecological surgeries.

Table 1: **Shows comparison of demographic and baseline characteristics between the three groups**

SN	Characteristic	Group D1 (n=25)	Group D2 (n=25)	Group D3 (n=25)	Statistical significance (ANOVA)
1.	Mean Age±SD (Years)	47.44± 9.69	44.80± 8.53	45.68± 8.98	F=0.548; p=0.581
2.	Mean BMI±SD (kg/m^2)	20.90± 2.44	20.93± 2.51	20.57± 2.09	F=0.178; p=0.837
3.	ASA Grade (No., %)				
	I	20 (80%)	20 (80%)	18 (72%)	χ^2=0.609; p=0.738
	II	5 (20%)	5 (20%)	7 (28%)	
4.	Mean Duration of surgery±SD (in min)	85.80±26.40	92.20±19.04	84.00±19.63	F=0.964; p=0.386

Table 2: **Shows comparison of different block characteristics in three groups**

SN	Variable	Group D1 (n=25)		Group D2 (n=25)		Group D3 (n=25)		Significance of difference	
1.	Peak level of sensory block (Median)	T6		T4		T4		χ^2=3.160; p=0.206 (Kruskall Wallis test)	
		Mean	SD	Mean	SD	Mean	SD	F	P
2.	Time taken to reach T10 level of sensory block	3.12	0.83	2.44	0.96	2.36	0.81	5.754	0.005
3.	Time taken to achieve motor block (Bromage score=3)	3.56	0.96	3.20	1.04	2.32	0.63	12.717	<0.001
4.	Time taken for regression of block by two segment	148.44	38.17	132.20	31.36	148.60	32.55	1.903	0.157
5.	Total time of sensory block (regression to S_1 level)	363.60	91.22	390.28	61.09	381.60	79.26	0.757	0.473
6.	Time taken to reach bromage score 0	233.80	62.67	205.52	45.42	246.56	59.63	3.465	0.037

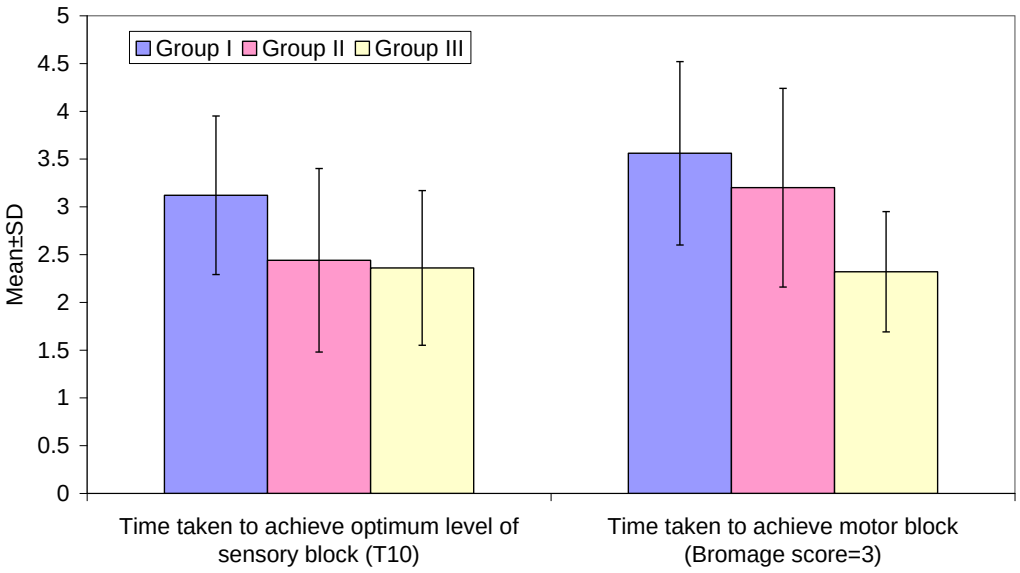

Fig 1: Comparison of different time taken to reach T_{10} level and bromage 3 in the three groups

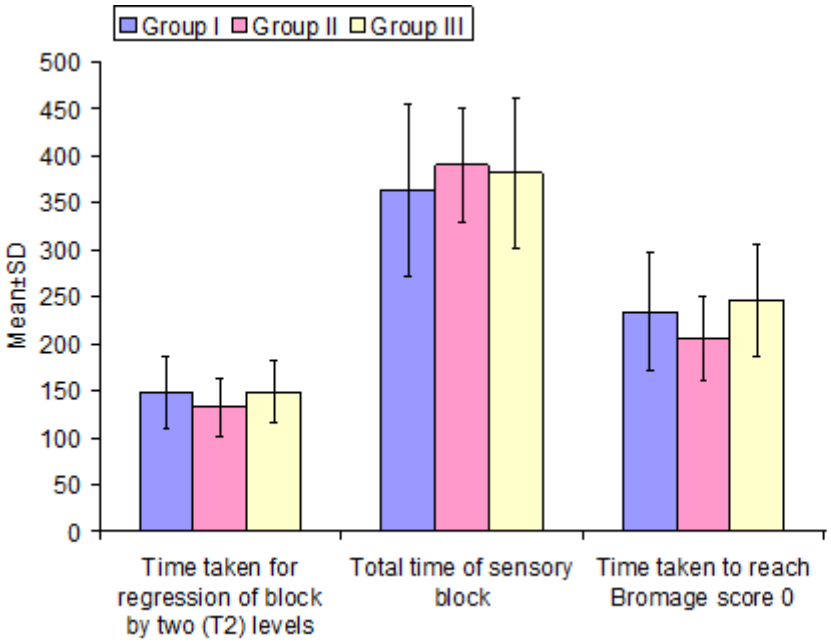

Fig-2: Comparison of different time durations for block to regress: by 2 segment, to S1, to bromage0 in the three groups.

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