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Original Research Article

Evaluation of opioid sparing effect of dexmedetomidine and pregabalin using acute pain model in male wistar rats

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ABSTRACT

Background: Adjuvant analgesics are added to pain management regimen to reduce opioid consumption and minimise their side effect. Newer ones like dexmedetomidine and pregabalin have not been thoroughly researched. Objectives of the study to study the opioid sparing effect of dexmedetomidine and pregabalin using tail flick and hot plate method in male wistar rats.
Methods: Forty two rats were grouped into seven groups with six in each group. Analgesic activity was tested using tail flick, where in the reaction time to flick its tail on a heated surface was noted. In the hot plate method, the reaction time to withdraw or lick the paws when placed on heated surface was noted.
Results: The reaction time to flick its tail was prolonged with dexmedetomidine and pregabalin when combined with opioids even in sub therapeutic doses.
Conclusion: Adjuncts like dexmedetomidine and pregabalin can be very useful in mutimodal pain management and also to reduce the opioid consumption.

Key words: Dexmedetomidine, Hot plate method, Pregabalin, Tail flick method

INTRODUCTION

Multimodal Analgesia in pain management is a rapidly upcoming treatment modality that aims to combine different analgesics that act by different mechanisms at different sites in the nervous system to provide synergistic effect, reduce the opioid consumption and lower the adverse effects of opioid analgesics.[1]

Opioids are the mainstay analgesics in pain management that produce undesirable adverse effects like respiratory depression, vomiting, mucle rigidity, acute tolerance and hyperalgesia. Hence adjuvant analgesics are added to reduce opioid consumption, commonly referred as "opioid sparing" effect.[2,3] Dexmedetomidine is a α_2 agonist approved by FDA as a sedative analgesic drug in intensive care unit, with very minimal respiratory depression and also reduces opioid tolerance.[4] Pregabalin is a structural derivative of gamma amino butyric acid that has analgesic, anticonvulsant and anxiolytic properties and used as an adjunct analgesic.[5]

The analgesic effect of dexmedetomodine has not been extensively studied as it is an recently introduced drug.

Moreover, dexmedetomidine and pregabalin can be used along with opioids to reduce their consumption and thereby side effects.

Hence we planned to study the opioid sparing effect of dexmedetomidine and pregabalin using tail flick and hot plate method in male wistar rats.

METHODS

After approval from the institutional animal ethics committee, 42 adult male Wistar rats were procured from TANVAS institute, Chennai and were housed in Central Animal House, Mahatma Gandhi Medical College and Research Institute, Pondicherry. As per the CPCSEA guidelines, the rats were housed 3 per cage with adequate bedding material and adequate social interaction were allowed.

The rats were allowed to acclimatize to the laboratory environment for a period of 1 week with alternate light dark cycle at room temperature of 22+2°C providing free access to food (pellet chow diet) and water ad libitum. There will be 7 groups with 6 rats in each group.

- Group I: Normal saline at dose of 10 ml/kg
- Group II: Fentanyl under trade name of Trofentyl procured from Troika pharmaceuticals(100 mcg/2ml); at a dose of 30mcg/kg
- Group III: Fentanyl under trade name of Trofentyl procured from Troika pharmaceuticals (100 mcg/2ml); at a dose of 15mcg/kg
- Group IV: Dexmedetomidine under trade name of Dextomid procured from Neon laboratories, Mumbai (100 mcg//ml) at dose of 60mcg/kg
- Group V: Pregabalin under trade name of Preglan procured from Speciality Meditech Pvt Ltd (10mg/ml) at dose of 30 mcg/kg
- Group VI: Combination of Fentanyl(15mcg/kg) and Dexmedetomidine (30 mcg/kg)
- Group VII: Combination of Fentanyl(15mcg/kg) and Pregabalin (15mcg/kg)

All the drugs were administered by intra peritoneal route. Dosages were chosen according to previous successful studies.

Tail flick method

The analgesic activity was tested by tail flick method, by radiant heat using analgesiometer, the standard method to test potency of centrally acting analgesic agents.[6]

The rat was placed in restrainer such that proximal third of tail was left behind. Radiant heat was delivered to proximal third of tail. After few seconds the rat was observed for flicking the tail. This reading was taken as the end point. This reaction time at which the rat flicks the tail was noted. Before giving the drug, the reaction time was noted as the baseline response. The drugs were administered according to the respective groups in respective dosages. Readings were taken at 30, 60, 90 and 120 minutes of giving the drug and the respective reaction times were noted.

Hotplate method

After a washout period of 15 days the rats were divided according to groups and the analgesic activity was tested by hotplate method.[7] The rats were placed on the hot plate which consists of an electrically heated surface at a temperature of 55-56 degree. Responses such as jumping, withdrawal of paws and licking of paws were seen. The reaction time period until the responses occurs were noted. Drugs were administered and the time period to produce any of these response were noted at 30, 60 and 90 and 120 minutes of administering the drug. All the observed data were recorded in Microsoft excel and statistical analysis was done using SPSS version 16 software.

RESULTS

The reaction times observed in estimating the analgesic effect using tail flick and hot plate method is tabulated in Tables 1 and 2. Mean SD was used to evaluate the mean value of the observations in each group. Opioid sparing effect of dexemedetomidine and pregabalin was analysed by ANOVA. $p<0.05$ was considered to be statistically significant. The results of the study revealed that both dexmedetomidine and pregabalin had good analgesic effect and the opioid sparing effect of reducing the opioid consumption was higher in dexmedetomidine than pregabalin in both tail flick and hot plate methods.

DISCUSSION

Opioids are the mainstay of postoperative analgesia and chronic pain. Its use is limited by the occurrence of dose related side effects like respiratory depression, nausea, vomiting, sedation etc. Hence many analgesics.[8] like clonidine, dexmedetomidine, steroids, diazepam are used as adjuncts in pain relief to overcome the limitations of opioids. In our study dexmedetomidine produced good analgesic effects even with less opioid dose revealing its opioid sparing effect. In our study, the reaction time period of dexmedetomidine 60mcg/kg in tail flick method was 4.92±0.17 min at the end of 90 minutes of administering the drug. When Fentanyl 15mcg/kg and Dexmedetomidine 30mcg/kg was administered to the rats, the reaction time was 4.80±0.22 minutes. Similar results were obtained in hot plate method also. This reveals that dexmedetomidine in sub therapeutic doses when combined with opioids produce good analgesic effect, thereby therapeutically useful as a analgesic adjunct in pain management. Also, it reduced the opioid consumption which is very useful in limiting the side effects of opioids like respiratory depression and tolerance leading to addiction when used chronically.

Table 1: Reaction time observed in tail flick method.

Groups	Drug dosage	Reaction time in minutes observed				
		Before the drug	30 mins after drug	60 mins after drug	90 mins after drug	120 mins after drug
I	Normal saline	0.76±0.02	0.76±0.02	0.78±0.01	0.78±0.02	0.77±0.29
II	Fentanyl 30 mcg/kg	0.78±0.09	2.10±0.36	3.02±0.40	4.02±0.33	4.01±0.22
III	Fentanyl 15 mcg/kg	0.80±0.02	2.90±0.25	3.20±0.29	4.94±0.23	4.98±0.24
IV	Dexmedetomidine 60 mcg/kg	0.82±0.01	3.06±0.18	4.59±0.10	4.92±0.17	4.38±0.22
V	Pregabalin 30 mcg/kg	0.74±0.03	0.74±0.08	0.78±0.09	1.92±0.86	2.80±0.25
VI	Fentanyl 15 mcg/kg and Dexmedetomidine 30 mcg/kg	0.76±0.03	3.10±0.06	4.80±0.22	5.05±0.28	4.89±0.25
VII	Fentanyl 15 mcg/kg with Pregabalin 15 mcg/kg	0.84±0.03	1.08±0.18	2.76±0.25	3.22±0.98	3.40±0.62

Comparison of groups 1,2,3,4,6: df=1,F=2.51, p=0.000.*** Comparison of groups1,2,3,5,7df=1,F=1.48,p=0.000**

Table 2: Reaction time observed in Hot plate Method.

Groups	Drug dosage	Reaction time in minutes observed				
		Before the drug	30 mins after drug	60 mins after drug	90 mins after drug	120 mins after drug
I	Normal saline	3.96±0.52	2.89±0.16	3.92±0.30	3.24±0.03	3.22±0.14
II	Fentanyl 30 mcg/kg	3.18±0.02	6.66±0.02	6.92±0.03	6.83±0.09	6.10±0.02
III	Fentanyl 15 mcg/kg	3.32±0.08	6.68±0.07	7.86±0.23	8.24±0.30	7.50±0.03
IV	Dexmedetomidine 60 mcg/kg	3.40±0.04	7.78±0.18	8.18±0.26	8.55±0.07	8.11±0.23
V	Pregabalin 30 mcg/kg	3.33±0.05	3.86±0.29	3.66±0.27	3.67±0.04	3.40±0.14
VI	Fentanyl 15 mcg/kg and Dexmedetomidine and 30 mcg/kg	3.22±0.04	7.41±0.27	8.22±0.23	8.66±0.30	8.19±0.30
VII	Fentanyl 15 mcg/kg with Pregabalin 15 mcg/kg	3.20±0.60	6.19±0.22	6.72±0.10	6.15±0.70	5.85±0.09

Comparison of groups 1,2,3,4,6: df=1,F=8.07, p=0.000***. Comparison of groups 1,2,3,5,7: df = 1,F=863.678,p=0.000**

Similar study by Mumin unal et al. who evaluated the synergistic potentiation effect of ineffective doses of dexmedetomidine on antinociception induced by morphine and fentanyl in acute pain model in rats reported that the analgesic effect of dexmedetomidine with morphine and dexmedetomidine with fentanyl, was significantly higher at 15, 30, 60 and 90 minutes after administration of the drug than either drug alone. [9]

This effect, thereby the opioid sparing effect of dexmedetomidine is attributed to α2 adrenegic agonistic action of dexmedetomidine on the presynaptic receptors thereby inhibiting the release of substance P. These receptors are abundant at the locus cereleus thereby responsible for the analgesic effect. The inhibition of substance P would be the the probable reason supporting the reduction of opioid requirements by dexmedetomidine.[10]

Neusa Maria et al, performed a study on the opioid consumption in total intravenous anesthesia(TIVA) in patients undergoing gynecologic video laparoscopic surgery and reported that dexmedetomidine is a very efficient drug in TIVA and opioid consumption is reduced. Moreover, in our study the reaction time period of Pregabalin 15mcg/kg with Fentanyl 15mcg/kg in tail flick method was 3.22±0.98 min at the end of 90 minutes of administering the drug. Similar results were obtained in hot plate method also. Unlike dexmedetomidine, this result was higher than pregabalin alone but not with standard drug fentanyl alone which reveals the weak analgesic effect and can be used as a potential analgesic adjunct in chronic pain, post-operative pain etc. [11]

Clendensen et al, performed a study on 50 patients undergoing rotator cuff repair and pregabalin 50 mg was prescribed orally twice a day. He observed that the mean opioid consumption was reduced when combined with pregabalin and he reported pregabalin to be a very useful adjunct in pain management.[12] This opioid sparing effect of pregabalin is probably due the reduction in the release of substance P by tight binding to the α2 subunit of calcium channels.[13] The credentials of this study will be validated only when performed in humans which is the major

limitation. Our study adds on to the information available to help the clinicians make a healthy decision.

CONCLUSION

As revealed by authors of the study, adjuncts like dexmedetomidine and pregabalin can be very useful in multimodal pain management and also to reduce the opioid consumption.

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