DEXMEDETOMIDINE: AS NOVEL PREMEDICATION
Priti Kolarkar¹, Gunjan Badwaik², Heena Pahuja³, Ajay Watve⁴, Jitendra Kalbande⁵, Yashashree Mukkirwar⁶, Nupur Bhangale⁷, Amol Bhalerao⁸

HOW TO CITE THIS ARTICLE:

ABSTRACT: Laryngoscopy and tracheal intubation causes intense autonomic reflex responses such as tachycardia, hypertension and a rise in intraocular pressure (IOP). Rise in IOP is further compounded by the use of succinylcholine. Various drugs used to attenuate the rise in IOP are pre-treatment with non-depolarizing muscle relaxant, lignocaine, narcotics, nifedipine and nitroglycerine, but none is found to abolish it completely. To obtain haemodynamic response lignicaine, opiods, nitroprusside, nitroglycerine, vearpamil, nifedipine, esmolol, clonidine etc. have been used. AIMS AND OBJECTIVES: We investigated whether dexmedetomidine an α₂ agonist could attenuate the rise in IOP after succinylcholine and intubation. Simultaneously, its effect on attenuation of haemodynamic response (Heart rate and MAP) to laryngoscopy and intubation was also evaluated. MATERIALS AND METHODS: Eighty patients without pre-existing eye disease undergoing general anesthesia was randomly premedicated by iv dexmedetomidine 0.6µg or saline. Heart rate (HR), mean arterial pressure (MAP), IOP (using Schioetz tonometer) was measured before, after the premedication, after thiopental, after succinylcholine, immediately after intubation and then every minute for 3 minutes. Statistical Analysis: descriptive and inferential statics using chi-square test, z- test and Wilcoxon sign rank test was done. Software used in the analysis was SPSS 17.0 version and Graph Pad Prism 5.0. Data was reported as mean value ± SD & p-value < 0.05 was considered as level of significance. RESULTS: Succinylcholine and intubation increased IOP in both the groups. However, in the dexmedetomidine group, it was not significantly different from baseline values (z value=0.93, p=0.358) and was significantly lower than in the control group (z =-6.644, p=0.000). After intubation the MAP in the control group (z=17.4, p=0.000) was higher than that in the dexmedetomidine group (z=8, p=0.000) and exceeded the baseline value (p<0.05). The heart rate also showed a less fluctuation in the dexmedetomidine group than in the control group. (z=7.73, p<0.05 after succinylcholine and z=9.22, p<0.05 after intubation) CONCLUSION: IV dexmedetomidine 0.6µg premedication is advantageous as it is found to be effective in reducing the rise in IOP. It is also beneficial in attenuating the haemodynamic response of succinylcholine, laryngoscopy and intubation to prevent its consequences. KEYWORDS: Intraocular pressure, dexmedetomidine, succinylcholine.

INTRODUCTION: The attendant danger of hypertension and tachycardia observed during laryngoscopy and intubation and rise in IOP which is further compounded by the use of suxamethonium, need considerable attention to prevent their consequences such as arrhythmia and myocardial ischemia in response to intense autonomic reflex and the rise in IOP can be deleterious to the patients with open globe injuries. Suxamethonium causes a transient but significant increase in IOP of about 10 mm of Hg lasting 1-10 min after injection, peaking at 2-4 min. Various other methods to attenuate this rise in IOP are pre-treatment with non-depolarizing muscle relaxant, lignocaine, narcotics, nifedipine and nitroglycerine. Various drugs used to obtund the
cardiovascular responses are lignocaine in various forms, high doses of opioids like fentanyl, alfentanil, sufentanil, buprenorphine etc, vasodilators like sodium nitroprusside, nitroglycerine, hydralazine, calcium channel blockers like verapamil, nifedipine, nitratepide, manidepine etc, alpha adrenergic blocker like droperidol, beta adrenergic blockers like metoprolol, esmolol, magnesium sulphate, alpha adrenergic agonist like clonidine\textsuperscript{5} and recently dexmedetomidine.\textsuperscript{6}

Dexmedetomidine, a highly selective $\alpha$-2 adrenergic agonist has sedative and analgesic effects.\textsuperscript{7,8} $\alpha$-2 agonists provide potentially beneficial effects in ophthalmic surgery because of their IOP lowering properties.\textsuperscript{9,10} The aim of our study is to evaluate the efficacy of IV dexmedetomidine pre-medication on IOP changes after succinylcholine administration and intubation. Simultaneously, its effect on attenuation of haemodynamic response (HR and MAP) to laryngoscopy and intubation was also evaluated.

**MATERIALS AND METHODS:** In this double-blind, randomized, controlled clinical trial, after approval from institutional ethical committee, and with written informed consent, eighty, adult, ASA class I or II patients scheduled for elective non-ophthalmic surgeries to be performed under general anaesthesia were recruited. Patients were excluded if had body weight more than 150% of their ideal body weight using Broca’s index, had acute or chronic eye disease, had Contraindication to study drug, were receiving any drug known to alter IOP, with obvious intubation difficulty, Pregnant or lactating patient, Hypertensive patients receiving any antihypertensive, had Psychiatric disorders.

Randomization was done by computer generated randomization table using Software “Minitab”, random sequence was generated by random allocation software. Patients were allocated into 2 groups; Group D (n=40) to receive a single bolus IV dose of dexmedetomidine (0.6 $\mu$gkg\textsuperscript{-1}) diluted up to 20 ml as pre-medication or Group C (n=40) to receive IV saline (20 ml) as pre-medication. A syringe containing pre-medication (either dexmedetomidine or normal saline) was prepared by a team member who was not involved in the data recording. Intraoperative monitoring included three lead ECG, plethysmographic pulse oximeter, capnography and non-invasive arterial pressure.

Intraocular pressure readings were measured using Schiotz tonometer with 5.5 gm weight attached to it. Same instrument was used throughout the study and observations were made by the same observer in all the patients so as to avoid observer bias. Topical 1 to 2 drops of 0.5% propcaine was instilled in the conjunctival sac for surface anesthesia of the cornea. Patients were pre-medicated with a single dose of dexmedetomidine 0.6$\mu$gkg\textsuperscript{-1} IV using 20ml syringe pump over 10 min in group D and the same amount of saline was given to the patient in the control group. Both the groups were also pre-medicated with IV fentanyl 1$\mu$gkg\textsuperscript{-1}.

After pre-oxygenation for 3 min both groups were induced with injection thiopental 5 mgkg\textsuperscript{-1}. Succinylcholine 2 mgkg\textsuperscript{-1} was administered. After ceasing of fasciculations gentle laryngoscopy done by the trained anesthesiologist and patient was then intubated with proper size cuffed endotracheal tube under direct vision. Correct position of tracheal tube was verified by auscultation of the chest and by capnometry.

It was decided to exclude those patients from the study who require more than one attempt for intubation. However, all the patients in our study were intubated in first attempt and there was no exclusion. Intraoperative lactated Ringer solution was administered at 4mlkg\textsuperscript{-1} h\textsuperscript{-1} iv. Further management of cases was done according to institutional protocol for general anaesthesia.
Hypotension (MAP ≤ 30% from baseline) was treated with IV ephedrine 6 mg and bradycardia (heart rate ≤ 30% from baseline) was treated with IV glycopyrolate 0.2 mg. Mean arterial pressure (MAP), heart rate (HR) and intraocular pressure (IOP) readings were taken at following time interval:
- T1: Baseline on OT table (after topical 0.5% procaine instillation to cornea).
- T2: 10 min after pre-medication.
- T3: 30 seconds after thiopental.
- T4: 30 second after succinylcholine.
- T5: immediately after intubation.
- T6-8: every 1 min for 3 min after intubation.

**STATISTICAL ANALYSIS:** Sample size was calculated by using EPI info software (3.4.3) in consultation with a statistician, minimum sample size was calculated 40 in each group, considering confidence interval of 95 %, power 90 % by 1:1 Unpaired T – test was used to find out significance between two samples. Data was reported as mean value ± SD & p-value < 0.05 is considered as level of significance. All the data were entered into the excel database from paper pro forma. During the data entry, data was checked for any error or missing data. After resolution of all issues, the database was analyzed. Statistical analysis was done by using descriptive and inferential statistics using Chi-square test, z-test and Wilcoxon sign rank test.

The software used in the analysis were SPSS 17.0 version and Graph Pad Prism 5.0. Randomization was done using software ‘Minitab’ (computer software) computer generated randomization. The comparison of normally distributed continuous variables between the groups was performed by Z-test and comparison of groups from baseline was done by Wilcoxon sign rank test. Nominal categorical data among study groups were compared using the chi-square test.

**RESULTS:** With regard to age, weight, gender, MPC grading, and baseline IOP, HR, MAP there were no significant differences between two groups (Table 1). In group D, after dexmedetomidine injection there was a significant decrease in IOP, compared with baseline (p= 0.000) There was a further significant decrease in IOP (P=0. 000) after thiopental injection. Succinylcholine and intubation increased IOP in group C (p=0. 006;p=0.000). However, in group D, there was a significant decrease after succinylcholine (p=0. 000) and was not significantly different from baseline after intubation (p=0. 358) unlike in the group C.

There was statistically significant initial fall in HR in group D after dexmedetomidine (p=0. 000). There was rise in HR, after thiopental, succinylcholine and intubation remaining raised till 2 min post-intubation in both the groups(p=0.000&0.017). But this rise was statistically significant in the control group from T2-T6 as compared to group D (p=0. 000; 0.001; 0.003; 0.000; 0.0140 at various levels from T2-T6). Heart rate in both groups was almost near to the baseline values at T7 and T8 (p=1. 000).

The MAP was increased significantly compared with the preoperative value after intubation in the group C (p=0. 000) and was significantly higher than in group D (p=0. 000). In the group D, MAP was not significantly higher than the preoperative value at all times. No incidence of hypotension or bradycardia requiring intervention was reported in both groups.
DISCUSSION: The pressor response associated with laryngoscopy and intubation are due to reflex sympatho-adrenal discharge provoked by epilaryngeal and laryngotracheal stimulation. It is also associated with increase in IOP due to increased sympathetic activity and resistance to outflow of aqueous humour in trabecular meshwork between anterior chamber and Schlemn’s canal. Dexmeditomidine premedication in ophthalmic surgery under local anaesthesia was effective in reduction of IOP.\textsuperscript{11,12}

Dexmeditomidine, may be having direct vasoconstrictor effect on the afferent blood vessels of the ciliary body resulting in reduction of aqueous humour production.\textsuperscript{13} Moreover, it reduces sympathetically mediated vasomotor tone of ocular drainage system leading to increased outflow of aqueous humour.\textsuperscript{14} Addionally associated haemodynamic response of Dexmeditomidine could contribute to IOP lowering effect.\textsuperscript{15}

This close relationship between haemodynamic and IOP response is also seen in our study. In group D, there was fall in MAP after T2 till T8 and at corresponding times there was reduction in IOP also. Blunting effect on rise of IOP caused by succinylcholine and intubation was main finding of our study. It was seen that succinylcholine and intubation increased IOP in both groups but IOP in dexmedetomidine group was not significantly different from baseline.

The rise in the group C was statistically on higher side than group D, where it appeared to be blunted with the use of dexmedetomidine. The IOP reducing effect of Dexmeditomidine, in our study is consistent with previous studies using a2 agonists clonidine.\textsuperscript{16,17,18} Similar IOP lowering effects of a single IV dose of dexmedetomidine (0.6 µg/kg\textsuperscript{-1}) was recorded after pre-medication and immediately after intubation in opthalmic\textsuperscript{9} and nonophthalmic\textsuperscript{6} surgeries. Lee et al\textsuperscript{19} could not find IOP lowering effect using dexmedetomidine infusion as supplement to isoflurane anaesthesia. This could be due to lower loading dose used by them in our study.

In our study, Additionally, Dexmeditomidine premedication attenuated haemodynamic response of laryngoscopy and intubation where HR and MAP increased significantly after intubation in group C whereas in group D this response was attenuated. Several previous studies have reported the blunting effect of Dexmeditomidine on the sympathetic response to laryngoscopy and intubation,\textsuperscript{6,10,20,21} This could be due to centrally mediated sympatholytic effects of a2 agonists and by its decreasing norepinephrine release via peripheral presynaptic a2 receptors\textsuperscript{22,23}

The dose of dexmedetomidine pre-medication administered in our study (0.6 µg/kg) was based on the previous clinical studies\textsuperscript{6,9,10} where the selected dose resulted in a significant reduction in IOP in response to intubation and the pressor response to laryngoscopy and endotracheal intubation was also significantly attenuated. Higher doses of dexmedetomidine were associated with an additional reduction in the arterial pressure and heart rate without any further decrease in the IOP\textsuperscript{24, 25}. With the use of lower doses of dexmedetomidine, neither the increase in BP during intubation could be attenuated nor could the rise in IOP be reduced.\textsuperscript{19}

There is controversy regarding use of succinylcholine in open ocular injuries as it may precipitate extrusion of intraocular contents since it rises IOP and may further endanger sight in that eye. Many drugs like pre-treatment with non-depolarizing muscle relaxant, lignocaine, narcotics, nifedipine and nitroglycerine\textsuperscript{4} have been used in an attempt to obtain this undesirable effect.

Neither self-taming nor administration of higher doses of non-depolarizing muscle relaxant prevents the rise in IOP associated with suxamethonium. Non-depolarizing muscle relaxants can result in non-ideal intubation conditions, IOP rise from mask application, longer time with insecure
airway and prolonged paralysis, for which sugammadex\(^2\) may be useful, but not yet launched in clinical use. No method has been found to be completely satisfactory.

Patient with penetrating eye injury may present with full stomach. Although regional anaesthesia is valuable alternative for management in such situation, it had traditionally been contraindicated in such patients because of potential to extrude intraocular contents via pressure generated by local anaesthetics. Combined topical anaesthesia with sedation in selected patients is reported.\(^2\) Regional anaesthesia with sedation is also used in selected cases.\(^2\) With improved anaesthetic agents and techniques, and general anaesthesia is being used increasingly, in an attempt to optimize conditions for intraocular surgery in such cases.

Goal of anesthesia in this scenario is to secure the airway by rapid sequence intubation (RSI) without affecting IOP. Since ideal replacement of succinylcholine for RSI situations is yet to come and in difficult airway cases with salvageable eye situations, its use is still agreed.\(^4\) Succinylcholine rises IOP is an accepted fact, but this rise can be attenuated with various pretreatments, moreover this increase in IOP, in unimportant when weighed against the risk of loss of airway, especially in difficult airway situations, where use of succinylcholine is mandatory to secure the airway, where dexmedetomidine pretreatment can be recommended, to reduce the IOP rise.

Limitation with potential advantage of using dexmedetomidine as an alternative agent to obtain IOP changes after succinylcholine and intubation is that it’s this very effect on IOP change cannot be isolated from its action on the haemodynamics since both these effects are parallel and having a causal relationship with each other.

We conclude that IV dexmedetomidine 0.6 µg kg\(^{-1}\) as pre-medication is effective in reducing the rise in IOP and in attenuating the hemodynamic response of succinylcholine, laryngoscopy and intubation.

It can be recommended that with the use of IV dexmedetomidine in the dose of 0.6 µg kg\(^{-1}\) as pre-medication can be advantageous especially where there is marked rise in IOP due to laryngoscopy and intubation, as it could be deleterious in patients with impending perforation of the eye, perforating injury, glaucoma, etc. Moreover, its attenuating effect on hemodynamic response of laryngoscopy and intubation can be beneficial to the patients who are already at risk of deleterious cardiac effects.
**Fig. 1:** Changes in IOP in the control and dexmedetomidine groups. Measurements were recorded before premedication (T1), 10 min after premedication (T2), 30 secs after thiopental (T3), 30 secs after succinylcholine (T4), immediately after intubation (T5) and 1, 2, 3, min after intubation (T6-8). Significant difference of IOP between control and dexmedetomidine group at T2-T7. At T4 and T5 the difference was significant as rise in control group was more.

![Fig. 1](image1)

**Fig. 2:** Changes in MAP in the control and dexmedetomidine groups. Measurements were recorded before premedication (T1), 10 min after premedication (T2), 30 secs after thiopental (T3), 30 secs after succinylcholine (T4), immediately after intubation (T5) and 1, 2, 3, min after intubation (T6-8). Significant difference of MAP between control and dexmedetomidine group at T2-T7. Rise was maximum at T5 in control group.

![Fig. 2](image2)

**Fig. 3:** Changes in HR in the control and dexmedetomidine groups. Measurements were recorded before premedication (T1), 10 min after premedication (T2), 30 secs after thiopental (T3), 30 secs after succinylcholine (T4), immediately after intubation (T5) and 1, 2, 3, min after intubation (T6-8). Significant difference of HR between control and dexmedetomidine group at T2-T7. Rise was maximum at T5 in control group.

![Fig. 3](image3)
**Fig. 3:** Changes in HR in the control and dexmedetomidine groups. Measurements were recorded before premedication (T1), 10 min after premedication (T2), 30 secs after thiopeptol (T3, 30 secs after succinylcholine (T4), immediately after intubation (T5) and 1, 2, 3, min after intubation(T6-8). Significant difference of HR between control and dexmedetomidine group at T2-T6. In control group significant continuous rise from T2-T5 and stability in dexmedetomidine group all throughout.

<table>
<thead>
<tr>
<th>Group C</th>
<th>Group D</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>39.0 ±10.23</td>
<td>42.22±12.25</td>
</tr>
<tr>
<td>MPC Grade I/II</td>
<td>23/17; 57.5%/42.5%</td>
<td>20/20; 50%/50%</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>53.25±7.77</td>
<td>53.10±8.50</td>
</tr>
<tr>
<td>Gender-Male/Female</td>
<td>19/21; 47.5%/52.5%</td>
<td>16/24; 40%/60%</td>
</tr>
<tr>
<td>Preoperative HR (beat min⁻¹)</td>
<td>75.713</td>
<td>74.807</td>
</tr>
<tr>
<td>Preoperative MAP (mm hg)</td>
<td>92 ± 12.52</td>
<td>94 ± 8.76</td>
</tr>
<tr>
<td>Preoperative IOP (mm hg)</td>
<td>14 ± 3.35</td>
<td>13.80 ± 2.29</td>
</tr>
</tbody>
</table>

Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>Group C</th>
<th>Group D</th>
<th>z-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>T2</td>
<td>13.80</td>
<td>3.89</td>
<td>12.00</td>
</tr>
<tr>
<td>T3</td>
<td>12.80</td>
<td>3.81</td>
<td>11.00</td>
</tr>
<tr>
<td>T4</td>
<td>16.00</td>
<td>4.13</td>
<td>12.50</td>
</tr>
<tr>
<td>T5</td>
<td>19.00</td>
<td>3.88</td>
<td>14.00</td>
</tr>
<tr>
<td>T6</td>
<td>14.00</td>
<td>2.96</td>
<td>12.40</td>
</tr>
<tr>
<td>T7</td>
<td>12.00</td>
<td>2.34</td>
<td>11.00</td>
</tr>
<tr>
<td>T8</td>
<td>11.00</td>
<td>2.08</td>
<td>11.00</td>
</tr>
</tbody>
</table>

Table 2: Comparison of IOP in both the groups using Z-test

<table>
<thead>
<tr>
<th>Group C</th>
<th>Group D</th>
<th>z-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>T2</td>
<td>95.00</td>
<td>12.55</td>
<td>88.00</td>
</tr>
<tr>
<td>T3</td>
<td>92.00</td>
<td>12.13</td>
<td>83.00</td>
</tr>
<tr>
<td>T4</td>
<td>95.00</td>
<td>11.19</td>
<td>83.00</td>
</tr>
<tr>
<td>T5</td>
<td>105.0</td>
<td>10.21</td>
<td>84.00</td>
</tr>
<tr>
<td>T6</td>
<td>84.00</td>
<td>8.56</td>
<td>76.00</td>
</tr>
<tr>
<td>T7</td>
<td>80.00</td>
<td>8.25</td>
<td>74.00</td>
</tr>
<tr>
<td>T8</td>
<td>78.00</td>
<td>7.78</td>
<td>75.00</td>
</tr>
</tbody>
</table>

Table 3: Comparison of MAP in both the groups using Z-test
<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th></th>
<th>Group D</th>
<th></th>
<th>z-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>75.00</td>
<td>7.13</td>
<td>74.00</td>
<td>8.07</td>
<td>0.58</td>
<td>0.559 NS, p&gt;0.05</td>
</tr>
<tr>
<td>T2</td>
<td>80.00</td>
<td>8.17</td>
<td>70.00</td>
<td>7.92</td>
<td>5.55</td>
<td>0.000 S, p&lt;0.05</td>
</tr>
<tr>
<td>T3</td>
<td>83.00</td>
<td>7.77</td>
<td>76.00</td>
<td>8.21</td>
<td>3.91</td>
<td>0.000 S, p&lt;0.05</td>
</tr>
<tr>
<td>T4</td>
<td>90.00</td>
<td>8.07</td>
<td>76.50</td>
<td>7.52</td>
<td>7.73</td>
<td>0.000 S, p&lt;0.05</td>
</tr>
<tr>
<td>T5</td>
<td>93.00</td>
<td>8.00</td>
<td>77.00</td>
<td>7.49</td>
<td>9.22</td>
<td>0.000 S, p&lt;0.05</td>
</tr>
<tr>
<td>T6</td>
<td>80.00</td>
<td>7.37</td>
<td>75.50</td>
<td>7.33</td>
<td>2.43</td>
<td>0.017 S, p&lt;0.05</td>
</tr>
<tr>
<td>T7</td>
<td>75.00</td>
<td>7.16</td>
<td>75.00</td>
<td>7.11</td>
<td>0.00</td>
<td>1.000 NS, p&gt;0.05</td>
</tr>
<tr>
<td>T8</td>
<td>74.00</td>
<td>6.99</td>
<td>74.00</td>
<td>6.63</td>
<td>0.00</td>
<td>1.000 NS, p&gt;0.05</td>
</tr>
</tbody>
</table>

Table 4: Comparison of HR in both the groups using Z-test

REFERENCES:
23. Lawrence CJ, Lange S. Effects of single single preoperative Dexmedetomidine dose on isoflurane requirements and perioperative haemodynamic stability. Anaesthesia 1997; 52; 736-44.
AUTHORS:
1. Priti Kolarkar
2. Gunjan Badwaik
3. Heena Pahuja
4. Ajay Watve
5. Jitendra Kalbande
6. Yashashree Mukkirwar
7. Nupur Bhangale
8. Amol Bhalerao

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Anaesthesia, NKP Salve Institute of Medical Sciences & Research Centre, Nagpur.
2. Assistant Professor, Department of Anaesthesia, NKP Salve Institute of Medical Sciences & Research Centre, Nagpur.
3. Assistant Professor, Department of Anaesthesia, NKP Salve Institute of Medical Sciences & Research Centre, Nagpur.
4. Assistant Lecturer, Department of Anaesthesia, NKP Salve Institute of Medical Sciences & Research Centre, Nagpur.
5. Senior Resident, Department of Anaesthesia, NKP Salve Institute of Medical Sciences & Research Centre, Nagpur.
6. Senior Resident, Department of Anaesthesia, NKP Salve Institute of Medical Sciences & Research Centre, Nagpur.
7. Junior Resident, Department of Anaesthesia, NKP Salve Institute of Medical Sciences & Research Centre, Nagpur.
8. Junior Resident, Department of Anaesthesia, NKP Salve Institute of Medical Sciences & Research Centre, Nagpur.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Priti Kolarkar,
Plot No. 287,
Ramnagar,
Nagpur-440033.
Email: pritisk8@gmail.com

Date of Submission: 05/08/2014.
Date of Peer Review: 06/08/2014.
Date of Acceptance: 11/08/2014.
Date of Publishing: 16/08/2014.