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Comparison of lidocaine versus dexmedetomidine in preventing propofol induced injection pain during induction of general anaesthesia in Chinese patient undergoing gynaecologic surgery: real world evidence.

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Abstract

Objective: To compare the efficacy and safety of lidocaine and dexmedetomidine in preventing propofol-induced pain in routine clinical practice.

Materials and methods: In this single center, prospective, non-interventional observational study, the women of ASA grade I or II with age between 18 to 65 years who were scheduled to undergo elective gynaecologic surgery under general anaesthesia with the use of propofol during 2010-2015 were enrolled. Patients received dexmedetomidine (0.2 mcg/kg, intravenously) and lidocaine (0.2 mg/kg, intravenously) at least 30 minutes prior to propofol injection (2 mg/kg) for induction during general anaesthesia. Pain after propofol injection was assessed from each patient after pre-treatment of lidocaine and dexmedetomidine using McCrirrick and Hunter scale for pain evaluation.

Results: A total of 1560 patients (778 patients in lidocaine groups and 782 patients in dexmedetomidine groups) were analysed. Both dexmedetomidine and lidocaine significantly decreased pain after administration of propofol in Chinese patents undergoing elective surgery. Significant reduction in pain score was found higher among patients who received lidocaine as compared to dexmedetomidine ($p<0.05$). Moreover, onset of analgesia after lidocaine injection was significantly shorter when compared dexmedetomidine among patients who received propofol ($p=0.04$). Approximately 65% of patients treated with lidocaine had no pain after propofol injection; this was significantly higher when compared with dexmedetomidine ($p<0.05$).

Conclusion: We suggest lidocaine is superior to dexmedetomidine in reducing propofol induced pain. Pre-treatment with intravenous injection of lidocaine was found better alternative to dexmedetomidine injection in management of propofol induced pain. Both the treatment is having acceptable safety profile.

Keywords: Lidocaine, Dexmedetomidine, Propofol, Pain, General anaesthesia.

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Introduction

Propofol is one of the most effective anaesthetic drugs from intravenous class of anaesthetic drugs. It is commonly indicated during general anaesthesia for induction and maintenance due to its rapid onset of action and short duration of action [1]. The most common adverse event induced by propofol is pain after propofol injection, the reported prevalence of injection pain following propofol injection varies from 25% to 100% [2,3]. Prevalence of propofol induced pain range from 28 to 90% among adults who received propofol injection in dorsum vein [4,5]. During induction phase of general anaesthesia, propofol induced pain causes stress among patients undergoing surgical procedure which results in poor procedural outcome due to use of propofol [6-8].

Injection pain following use of propofol was considered as 7th most significant difficulty experienced by clinical anaesthesia during general anaesthesia [9]. Pain after propofol injection is mainly due to the presence of phenol group in propofol. It is well known that phenol group causes irritation to mucus membrane and intima of vein which results in development of pain sensation [10].

There are several techniques available to reduce the severity of propofol induced pain included application of topical nitroglycerine at the site of injection, addition of dextrose 5% or opioids or non-steroidal anti-inflammatory agents with propofol as diluting agent. Among the available treatment option, use of intravenous lidocaine is increased to prevent propofol induced pain at the site of injection. Lidocaine is administered along with propofol or before administration of propofol in order to reduce the pain after propofol injection. There are few clinical evidences showing failure of lidocaine in reducing pain after propofol injection [6,11].

Dexmedetomidine is selective and potent alpha-2 receptor agonist and gaining attention of anaesthesiologist due to its

diverse pharmacological actions such as sedative, analgesic and sympatholytic. In addition to this, it has effect on spinal, supraspinal and peripheral region which potentiates its pharmacological actions. Dexmedetomidine inhibits release of Noradrenaline (NA) by activating alpha-2 receptor which results in production of Prostaglandin (PG) and subsequent release of PG causes vasodilation that provoke the vasoconstriction response lead to central level of antinociception [12]. Dexmedetomidine is also having peripheral anti-nociception action [13]. Hence, Dexmedetomidine can be used in decreasing the severity of propofol induced pain.

We routinely use dexmedetomidine and lidocaine as pre-medication in our hospital to prevent pain after propofol injection among Chinese patients undergoing gynaecologic surgery at our hospital. Due to lack of comparison of pain reliving capability of dexmedetomidine and lidocaine among Chinese patients, this encourages us to compare the pain reliving effect of dexmedetomidine and lidocaine after propofol injection among Chinese patients.

Materials and Methods

This single center, non-interventional prospective observational study designed to compare the efficacy of Lidocaine and Dexmedetomidine in reducing propofol-induced pain. In this study, female patients with age between 18 to 65 years who were scheduled to undergo elective gynaecologic surgery under general anaesthesia with the use of propofol and fentanyl as induction anaesthesia were selected, and all the patients were fall into American Society of Anaesthesiology (ASA) grade I or II. This study was performed at Department of Anaesthesiology, Maternal and Child Health Care Hospital of Hainan, China. Institutional ethics committee was obtained, and written consent was taken from each patients. Each enrolled patients in the study were explained about the study procedure, and potential benefits to the society associated, and duly signed declaration of the subjects were taken on information consent form. We have excluded the patients with ASA grade $\geq$ III; patients who requiring rapid sequence induction and the patient who are not willing to participate in this observational study. The patients who received dexmedetomidine 0.2 mcg/kg intravenously as pre-anaesthetic medicine during general anaesthesia were called dexmedetomidine group. The patients who received lidocaine 0.2 mg/kg intravenously as pre-anaesthetic medicine during general anaesthesia were called dexmedetomidine group. Dexmedetomidine and lidocaine were given to patients before at least 30 minute prior to administration of intravenous injection of propofol and fentanyl. Standard dose of propofol (2 mg/kg) was administered to each patient for induction during general anaesthesia. Pain reliving effect of dexmedetomidine and lidocaine after propofol injection was compared using McCrirrick and Hunter Scale for pain evaluation. All the study drugs were stored at as per their respective labelling instruction, and were prepared freshly using normal saline immediately before administration.

A standardized cannula (20-G) was inserted in vein and infusion rate was set on 2 ml in every 5 seconds). Propofol (2 mg/kg) was administered intravenously after completion of isotonic saline until the loss of consciousness. Pain was assessed using four point pain measurement scale (McCrirrick and Hunter Scale) from 0 to 3 where 0 indicates none and higher score indicates increased pain response. In McCrirrick and Hunter Scale, 0 indicates no pain (there was no response of question asked for pain); 1=mild pain reported in response to the question asked for pain with no behavioural signs; 2=moderate pain reported in response to question asked for pain with behavioural signs or patient reported pain immediately without questioning and 3=severe pain response with strong verbal response with facial grimacing or tears.

Data from each patient was coded and analysed using Graph Pad Prism statistical analysis software (version 6.0). Quantitative variable was presented as mean ± standard deviation, and data were compared using parametric/non-parametric statistical test based number of comparison group and distribution of data, using 2 sided statistical tests. Normality test (Kolmogorov-Smirnov test or Shapiro-Wilks test) will be used to check the distribution of data of quantitative data. Categorical variables was presented as absolute number and/or percentage of subjects in each category, and were compared using Chi-square or fisher exact test based on size of data, using 2 sided statistical tests.

Results

We have collected data of five year (2010-2015) from our hospital in this real world perspective observational study. Total 1780 Chinese female patients were identified and contacted who had scheduled to undergo gynaecological surgery were enrolled. Of these, total 1560 patients (778 patients in lidocaine groups and 782 patients in dexmedetomidine groups) met eligibility criteria and completed pain assessment after administration of propofol injection, and subjected in statistical analysis. The average (SD) age of patients was 42.4 (6.5) year and 43 (5.3) year in lidocaine and dexmedetomidine group, respectively (Table 1).

Proportion of patients with high body mass index (more than 25 kg/m^2 but less than 3025 kg/m^2, overweight patients) were slightly higher in lidocaine group than dexmedetomidine, however, statistical analysis shown that the difference between both the treatment group was not statistically significant. Body mass index was also found almost similar among individuals of both the groups. Type of gynaecological surgery performed between both the treatment groups is almost similar, with no clinically significant difference ($p>0.05$). Overall demographic and clinical characteristic of patients of both the group were comparable at baseline (Table 1).

Both dexmedetomidine and lidocaine significantly decreased pain after administration of propofol in Chinese patents undergoing elective surgery. However, significant reduction in pain score was found higher among patients who received lidocaine as compared to dexmedetomidine ($p<0.05$).

Moreover, the onset of analgesia after intravenous injection of lidocaine was significantly shorter when compared dexmedetomidine among patients who received propofol ($p<0.05$). In either group, none of patients experience severe pain after administration of propofol injection. The incidence of pain after propofol injection was significantly lower in lidocaine group than dexmedetomidine group (Table 2). In lidocaine group, significantly greater proportion of patients experienced no pain after propofol injection than dexmedetomidine group. A total of 65% of patient from lidocaine group had no pain after administration of propofol injection, whereas in dexmedetomidine group, 45% of patients experienced no pain after propofol injection. In lidocaine group, total of 26% of patients experienced mild pain after propofol injection, whereas in dexmedetomidine group, 35% of patients had mild pain (Table 2). The difference in proportion of patients with no pain and mild pain cases among both the treatment group was statistically significant, favouring the effect of lidocaine. Similar trend was observed when comparison was made between both the treatment groups for proportion of patients with moderate pain score after propofol injection.

In lidocaine group, there was significant lesser number of patients who had moderate pain after propofol injection as compared to dexmedetomidine group. A total of 10% of patients of lidocaine group experienced moderate pain, whereas moderate pain was observed in 20% of patients of dexmedetomidine group. Overall, pain after propofol injection was significantly lesser in patients who received intravenous lidocaine before administering propfol. Dexmedetomidine also reduced pain after propofol injection; however, the reduction was significantly greater in individuals who received lidocaine. The number of patients with pain after propofol injection was less in lidocaine group than dexmedetomidine group.

We also evaluated safety of lidocaine and dexmedetomidine in Chinese patients undergoing elective surgery over the period of 5 year. There are very few cases (less than 2%) of oedema, redness and wheal response was reported at the site of injection in both the treatment groups. Both the treatment having acceptable safety profile in real clinical practice. Both the treatment was found to be efficacious, safe and well tolerable in routine clinical practice.

Table 1. *Demographic and clinical characteristic of patients undergoing gynaecological surgery.*

Parameter	Lidocaine group (N=778)	Dexmedetomidine group (N=782)	P value
Age, year Mean (SD)	42.4 (6.5)	43 (5.3)	>0.05
BMI (kg/m^2) Mean (SD)	26.2 (2.8)	28.7 (3.3)	>0.05
Type of gynaecological surgery (%)			
Cervical cryosurgery	12%	8%	>0.05
Myomectomy	18%	15%	
Hysterectomy	22%	20%	
Dilatation and curettage	8%	5%	
Cystectomy	15%	12%	
Salpingostomy	20%	18%	
Vulvectomy	5%	22%	

Values are expressed as % of subjects in each category except age and BMI. N=Total number of subject in each group.

Table 2. *Number of patients with severity of pain score.*

Severity score (On McCrirrick and Hunter scale)	Lidocaine group (N=778)	Dexmedetomidine group (N=782)	P-value
0 (None)	510 (65.5%)	350 (44.75%)	
1 (Mild)	201 (25.8%)	272 (34.78%)	<0.05
2 (Moderate)	75 (9.64%)	197 (25.19%)	
3 (Severe)	0	0	

N=Total number of subject in each group.

Discussion

To the best of our knowledge, this was the first largest real world observational study to compare efficacy and safety of lidocaine against dexmedetomidine in propofol induced pain in china. The patients who received lidocaine intravenously experienced significantly greater pain reduction than dexmedetomidine after propofol injection. Approximately 65% of patients treated with lidocaine had no pain after propofol injection; this was significantly higher when compared with dexmedetomidine. Looking at the extensive use of propofol as intravenous injection in routine clinical practice, pain after propofol injection during induction phase of anaesthesia can't be ignored. Pain during induction anaesthesia is considered as 7th most significant difficulty during general anaesthesia [9]. It is well know that the pain is mainly due to the presence of phenol group in propofol and it causes irritation to mucus membrane and intima of vein which results in development of pain sensation. Several methods are available to reduce the severity of propofol induced pain and patients discomforts, this included application of topical nitroglycerine at the site of injection, and addition of dextrose 5% or opioids or non-steroidal anti-inflammatory agents with propofol as diluting agent. Among the available treatment option, use of intravenous lidocaine and dexmedetomidine to prevent propofol induced pain at the site of injection are increasing in our hospital. We therefore designed this real world study to compare the efficacy and safety of lidocaine and dexmedetomidine among Chinese patients. In our study, significant reduction in pain score was observed in lidocaine group than dexmedetomidine. Significantly greater reduction in pain and rapid onset action of lidocaine was possibly due to strong localized action of lidocaine, which prevents irritation of skin, mucus membrane and nerve ending within the vein which results in blocking generation of local pain sensation. It was interesting to note that the incidence and severity of

propofol induced pain was significantly lesser with lidocaine when compared to dexmedetomidine. In earlier studies, pre-treatment of dexmedetomidine failed to reduce the pain sensation after intravenous injection of propofol [14]. In contrast to this report, our study results showed that dexmedetomidine was effective in decreasing pain after propofol injection but at lesser extent as compared to lidocaine. Our finding about the efficacy of dexmedetomidine was consistent with the previous reports of Uzun et al. which showed that administration of dexmedetomidine before propofol injection was found effective in alleviating propofol induced pain [15]. In our study, the onset of analgesia was found is longer in patient treated with dexmedetomidine, which possibly due to its central nervous system mechanism. Dexmedetomidine is a potent alpha-2 receptor agonist and inhibits central level of nociception in management of propofol induced pain [12]. In our hospital, we routinely use dexmedetomidine and lidocaine as pre-medication to prevent pain after propofol injection among Chinese patients undergoing gynaecologic surgery. Our study compared the pain reliving capability of dexmedetomidine and lidocaine among Chinese patients; and suggested that lidocaine is superior to dexmedetomidine in reducing propofol induced pain. Oedema and redness at the site of injection was observed in few of patients of both the treatment. Both the treatment is having acceptable safety profile. Overall, both the treatments were safe and well tolerable.

Conclusion

Our study results suggested superiority of lidocaine over dexmedetomidine in reducing propofol induced pain. Pre-treatment with intravenous injection of lidocaine was found better alternative to dexmedetomidine injection in management of propofol induced pain. Both the treatment is having acceptable safety profile. Intravenous injection of lidocaine was found better alternative to dexmedetomidine injection in management of propofol induced pain. Both the treatment is having acceptable safety profile. Overall, both the treatments were safe and well tolerable.

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