Int J Clin Exp Med 2016;9(8):15494-15501
www.ijcem.com /ISSN:1940-5901/IJCEM0022595

Original Article

Association of catechol-O-methyltransferase val158Met polymorphism with postoperative analgesic opioid use

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Received December 23, 2015; Accepted June 8, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: This meta-analysis was performed to assess the effects of COMT rs4860 polymorphism on postoperation analgesia with opioid consumption. We conducted a search of all papers using PubMed, the Cochrane Library, EMbase, Ovid, Web of Science, Google (scholar), Chongqing VIP database, CBMDisc, and CNKI database. The fixed or random effect model was determined according to the heterogeneity among researches. The crude standardized mean difference (SMD) with 95% confidence interval (CI) was calculated. Publication bias was estimated using funnel plots and Begg's and Egger's test. Five studies involving 517 cases were included in this meta-analysis. The results indicated that cases with AA homozygote of the COMT rs4860 polymorphism required less opioid doses to achieve adequate pain relief, compared with those carrying the G allele (AG+GG) in 24 h after operation (SMD=-0.33, 95% CI -0.56, -0.10, P=0.005). Nevertheless, there were no statistically significant differences between an AA homozygote and a G carrier (AG+GG) in opioid doses in 48 h after operation (SMD=-0.01, 95% CI -0.35, 0.33, P=0.94) and pain score at 24 h after operation (SMD=-0.09, 95% CI -0.33, 0.15, P=0.47). There were no statistically significant differences between an AA homozygote and a G carrier (AG+GG); Future studies should be undertaken to ascertain any contribution of this polymorphism in opioid consumption in postoperative conditions.

Keywords: Catechol-O-methyltransferase, postoperation analgesia, polymorphism, meta-analysis

Introduction

Nowadays, Opioid such as morphine and Fentanyl has been widely used in postoperation pain control and showed well effects [1]. However, the consumption of opioid in postoperation pain control varies widely among individuals [2] and the reason remains unclear even considering other factors such as heredity, sex, age, weight and organ function [3]. Under these circumstances, there were many candidate genes approaches in effect of opioid consumption on postoperation pain control including Catechol-O-Methyltransferase (COMT) gene.

The chromosomal allocation of COMT gene is 22q11.2, which encodes the COMT protein. Reports have suggested that the important role of COMT single-nucleotide polymorphisms (SNPs) is played in affecting an individual's sensitivity to pain. COMT SNPs comprising rs4633, rs4818, rs6269 and rs4680, and rs4680 (G1947A (Val158Met)) were widely researched. Previous study, having compared opioid doses required by AA homozygote patients with those required subjects carrying G allele, has shown that AA patients need lower average opioid doses compared to other subjects [4]. In addition, there was a significant difference in opioid doses among the three protein-coding (AA vs. AG vs. GG) genotypes in 24 h postoperation. However, other studies have also revealed that no significant differences of opioid need are observed among different rs4680 SNPs at 24 h after operation [5-8]. accordingly the outcomes of individually published researches were limited and rather conflicting.

Because one single study may be not comprehensive enough to provide all reliable outcomes, this meta-analysis was performed on

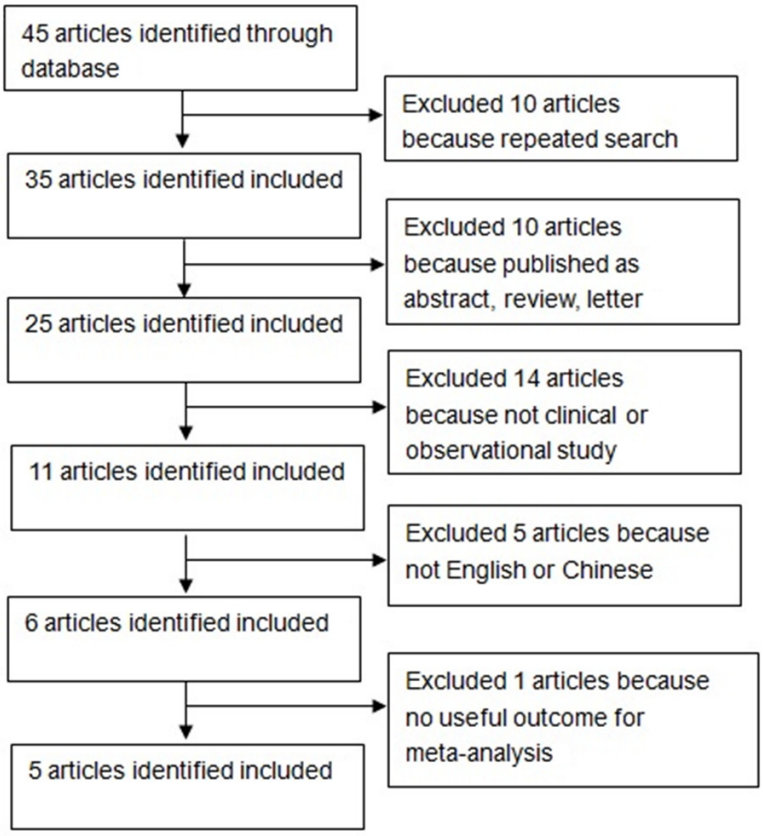

Figure 1. Flow chart demonstrating those studies that were processed for inclusion in the meta-analysis.

those eligible researches, in order to evaluate the precise effects of COMT rs4860 polymorphism on postoperation analgesia with opioid doses, which would have a much greater possibility of reaching reasonably sound conclusions.

Materials and methods

Literature search strategy

Two reviewers (Jinghua Jiao and Xiaoguang Chen) independently scrutinized studies on the effects of COMT rs4860 polymorphism on postoperation analgesia with opioid doses. We searched PubMed, the Cochrane Library, EMbase, Ovid, Web of Science, Google (scholar), Chongqing VIP database, Chinese Biological Medicine, China National Knowledge Infrastructure, Wan Fang Data and Chongqing VIP database (Last search was updated on OCT 19, 2015), using the terms ("single nucleotide polymorphism" or "SNP" or "polymorphism" or "gene mutation" or "genetic variants") and ("Catechol-O-Methyltransferase" or "COMT") and ("Fentanyl" or "Fentora" or "Phentanyl" or "Fentanest" or "morphine" or "R-4263" or "Duragesic"). Pub-Med option "Related Articles" was used for each study to search additional potentially relevant studies. Reference lists or textbooks were reviewed manually. We searched articles without language restriction, but only English or Chinese articles were contained in this meta-analysis.

Selection criteria

Studies were selected if they met the following criteria: (1) relevant study with the effects of COMT rs4680 polymorphism on postoperation analgesia with opioid; (2) sufficient data for COMT gene mutations with effects of postoperation pain control, using a prospective or observational design; (3) all cases received postoperation analgesia with opioid (fentanyl or morphine) for pain relief; and (4) the most complete (sufficient data) and latest results of the researchers with multiple publications.

Exclusion criteria

The exclusion criteria were defined as: 1) abstracts, letters, reviews, editorial articles or none clinical studies; 2) incomplete data, genotype number or frequency not reported; 3) duplicates of previous publications.

Data extraction

Data from the chosen studies were extracted independently by two reviewers (Jinghua Jiao and Xiaoguang Chen) into a standardized database. When discrepancies were appeared, all authors were recruited to assess the data. The following information was collected: first, author, publication year, country, ethnicity, sample sizes of cases, numbers of genotype and other characteristics.

Table 1. Characteristic of included studies

First author	Publication Year	Country	Ethnicity	Case number (n)	Age (year)	Study design	ASA physical status	Surgery	Genotype method	SNP ID	Opioid	Evaluating indicators	NOS score
Kolesnikov Y, et al. [5]	2011	Estonia	Caucasian	102	54.6±11.1	Prospective, observational	I/II	Abdominal surgery	PCR	rs4680 (Val158Met)	Morphine	Morphine dose for 48 h	6
												Pain score for 24 h	
												Nausea score	
												Sedation score	
												Antinausea drugs	
Tang QP, et al. [6]	2008	China	Asian	39	46.49±13.86	Observational	I/II	Abdominal surgery	PCR	rs4680 (Val158Met)	Fentanyl	Fentanyl dose for 24 h	6
Zhang F, et al. [7]	2015	China	Asian	115	20-75	Observational	I/III	Radical gastrectomy	PCR	rs6269	Fentanyl	Fentanyl dose for 24 h	6
										rs4680		Fentanyl dose for 48 h	
										rs4633		VAS pain score at 24 h	
										rs4818		VAS pain score at 48 h	
Candiotti KA, et al. [8]	2014	USA	Caucasian	152	NA	Observational	I/III	Elective nephrectomy	TaqMan assay	rs4680 (Val158Met)	Morphine	Opioid consumption for 24 h	6
												Pain score for 24 h	
Derisory M, et al. [9]	2013	Italy	Caucasian	109	18-75	Observational	NA	Abdominal/ urological	PCR	rs4680 (Val158Met)	Morphine	Opioid consumption for 24 h	6
										rs6269			
										rs4818			
										rs4633			

PCR: polymerase chain reaction. N/A: Not applicable. NOS, Newcastle-Ottawa score. SNP: single-nucleotide polymorphism.

Table 2. COMT Genotype (rs4680) frequency for included studies

First author	COMT Genotype (rs4680)				HWE
	Val/Val (GG)	Val/Met (GA) Val/Met (GA)	Met/Met (AA)	Val/Val (GG)+Val/Met (GA)	
Kolesnikov Y, et al. [5]	26	54	22	80	E
Tang QP, et al. [6]	21	11	5	32	E
Zhang F, et al. [7]	55	47	13	102	E
Candiotti KA, et al. [8]	31	60	61	91	NE
Deregori M, et al. [9]	26	50	33	56	E

HWE: Hardy-Weinberg equilibrium. COMT: Catechol-O-Methyltransferase. E: Equilibrium. NE: Not equilibrium.

The review and analysis were guided by the PRISMA statement [9].

Statistical analysis

The crude standardized mean difference (SMD) with 95% confidence interval (CI) was calculated. Hardy-Weinberg equilibrium was evaluated by the chi-square test. Heterogeneity was examined with *I* square statistic interpreted as the proportion of total variation contributed by between-study variation. If there was a statistical heterogeneity ($P<0.10$, $I^2>50\%$), the random effects model (Der Simonian and Laird method) would be utilized to estimate the SMD [10, 11]. Otherwise, we applied fixed effects model (Mantel-Haenszel method) to doing the analysis [12]. The possible publication bias was assessed with funnel plots and Egger's test and Begg's test. An asymmetric plot suggests a possible publication bias and the *P* value of Egger's test or Begg's test less than 0.05 was considered representative of significant publication bias [13]. All statistical tests were performed with STATA Version 11.0 software (Stata Corp., College Station, TX). A 2-tailed $P<0.05$ for any test was considered to be statistically significant.

Results

Study inclusion and characteristics

After review, five researches (involving 517 cases) meet the inclusion criteria and were included in the meta-analysis [4-8]. The detailed screening process is shown in **Figure 1**. The studies identified and their main characteristics and genotype number were summarized in **Tables 1** and **2**.

Quantitative data synthesis

As shown in **Table 3**, the results illustrated that r less opioid doses are required for the cases with AA homozygote of the COMT rs4860 polymorphism to alleviate pain adequately in comparison with those carrying the G allele (AG+GG) in 24 h after operation (SMD=-0.33, 95% CI -0.56, -0.10, P=0.005) (**Figure 2**). In addition, a significantly statistic difference was identified between AA vs. GG homozygote with opioid doses to control postoperation pain in 24 h (SMD=-0.48, 95% CI -0.76, -0.20, P=0.001). Nevertheless, there were no statistically significant differences between an AA homozygote and a G carrier (AG+GG) in opioid doses in 48 h after operation (SMD=-0.01, 95% CI -0.35, 0.33, P=0.94) and pain score at 24 h after operation (SMD=-0.09, 95% CI -0.33, 0.15, P=0.47).

There was no heterogeneity between studies and no significant publication bias according to Egger's (**Figure 3**) and Begg's tests (**Figure 4**) (Begg, P=0.73; Egger, P=0.53). The funnel plot was symmetrical as seen in **Figure 5**.

Discussion

To the best of our knowledge, it is the first meta-analysis to make the evaluation of the effects of COMT rs4860 polymorphism on postoperation analgesia with opioid. Previous report have investigated the association between COMT gene polymorphism and chronic human pain using meta-analysis [14] and indicated that chronic pain like fibromyalgia or chronic widespread pain was related to the COMT SNPs rs4680. In previous clinical studies, low COMT activity has been linked to the increased sensitivity to postoperative pain [15]. In order to discover the mechanism, several studies have tested the functional effects of COMT rs4860 polymorphism on postoperative pain control with fentanyl or morphine, but their results have been inconclusive [4-8].

In our meta-analysis, five clinical observational studies were included with a total of 517 cases who received postoperation analgesia with opioid. The results of this meta-analysis demonstrated that there was a relationship between

Table 3. Summary SMD and 95% CI of the effects of Catechol-O-Methyltransferase (COMT) rs4860 polymorphism on the opioid consumption for postoperation analgesia

	24 h opioid doses	24 h pain scores	48 h opioid doses
AA Homozygotes vs. G-carriers			
No. of Studies	4	3	3
No. of AA	112	96	40
No. of AG+GG	301	273	214
SMD (95% CI)	-0.33 (-0.56, -0.10)	-0.09 (-0.33, 0.15)	-0.01 (-0.35, 0.32)
P value	0.005	0.47	0.94
Heterogeneity, I^2 (%)	0	24.2	0
AA vs. AG			
No. of Studies	4	3	3
No. of AA	112	96	40
No. of AG	133	161	112
SMD (95% CI)	-0.23 (-0.47, 0.02)	-0.11 (-0.32, 0.21)	0.01 (-0.35, 0.37)
P value	0.06	0.67	0.94
Heterogeneity, I^2 (%)	0	0	0
AA vs. GG			
No. of Studies	4	3	3
No. of AA	112	96	40
No. of GG	133	112	102
SMD (95% CI)	-0.49 (-0.77, -0.20)	-0.06 (-0.32, 0.21)	-0.05 (-0.43, 0.33)
P value	0.001	0.49	0.79
Heterogeneity, I^2 (%)	42.1	0	0

SMD: standardized mean difference; CI: confidence interval.

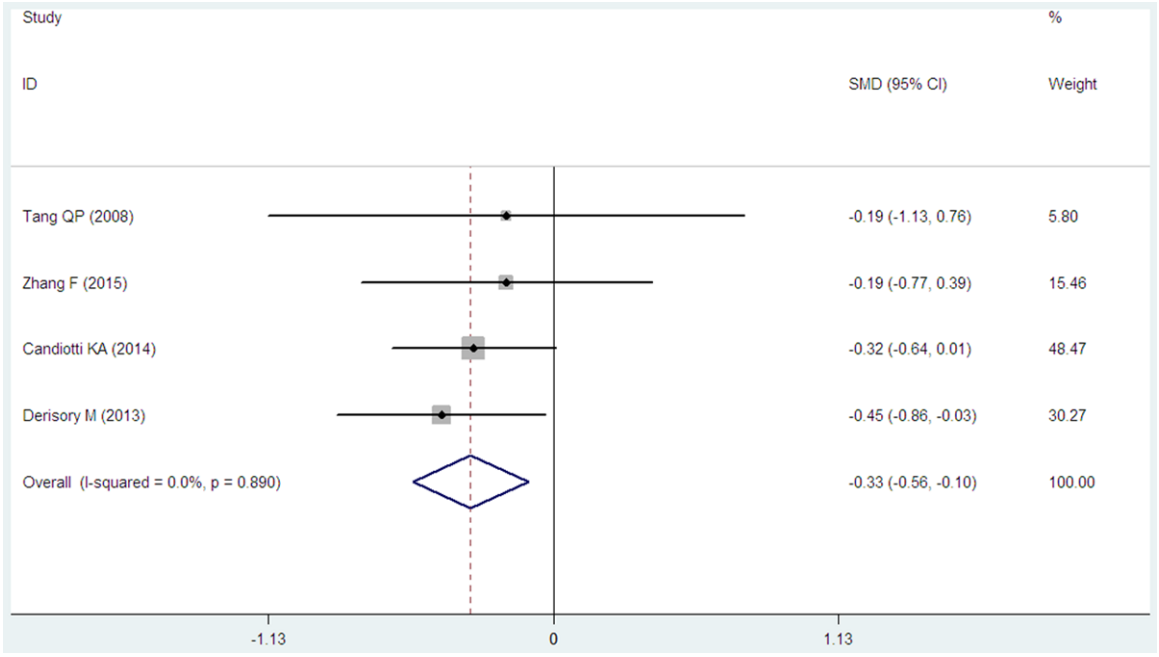

Figure 2. Forest plot for the effects of Catechol-O-Methyltransferase (COMT) rs4860 polymorphism on the opioid consumption for postoperation analgesia (AA vs. AG+GG).

COMT rs4860 polymorphisms and doses of opioid in 24 h after operation. Cases with AA homozygote of the COMT rs4860 polymorphism demanded less opioid doses to adquate pain control (there is no difference between AA vs. AG+GG or AA vs. GG or AA vs. AG groups on

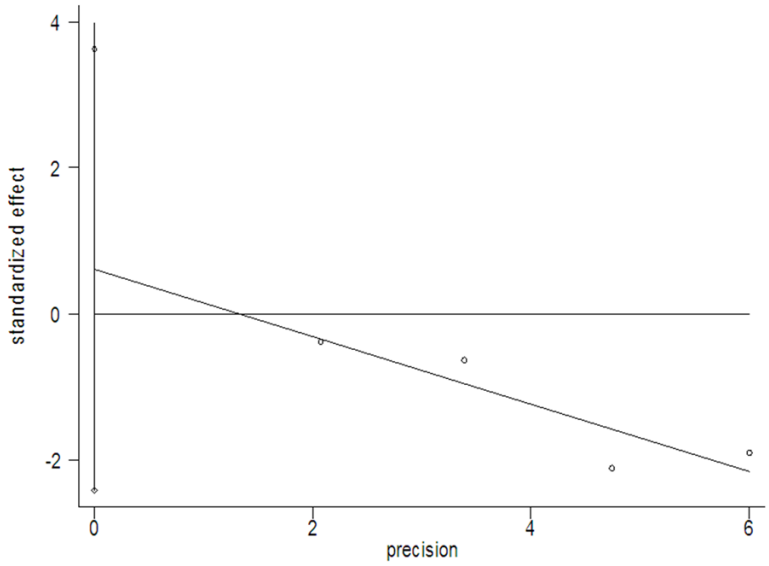

Figure 3. Egger's publication bias plot (AA vs. AG+GG).

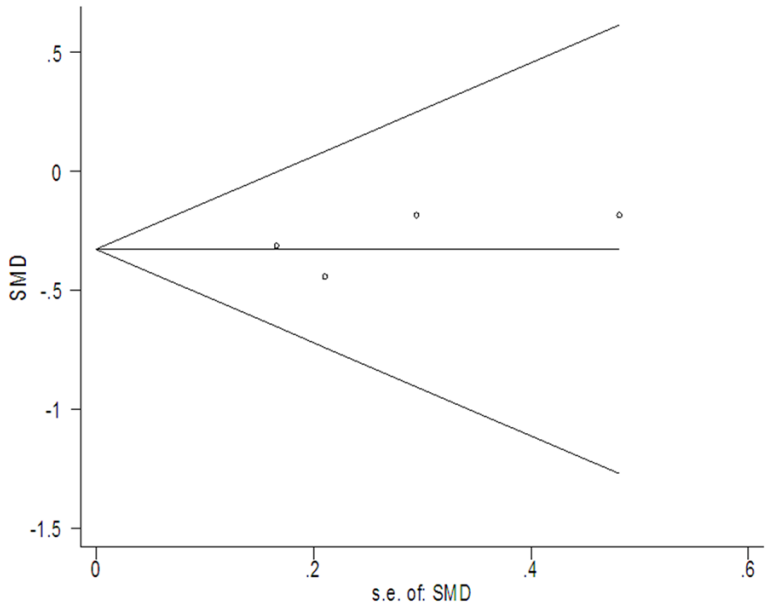

Figure 4. Begg's funnel plot with pseudo 95% confidence limits (AA vs. AG+GG).

pain score at 24 h after operation) compared with those carrying the G allele (AG+GG) in 24 h after operation. Only one study reported that there was no s difference with tatistical significance on pain score at 48 h after operation among genotype groups [7]. So the opioid consumption and pain score were the same at 48h after operation among COMT rs4860 genotype groups. These notable results could be deduced at list: 1) the same opioid consumption among COMT rs4860 genotype groups, based on the pain relief after 24 h postoperation, 2) the same opioid consumption from 24 h to 48 h postoperation, in accordance with the same pain score at 24 h postoperation achieved by distinct COMT rs4860 genotype cases. In any case, according to this meta-analysis result, clinical doctor could use less opioid consumption to achieve pain control for cases with AA homozygote of the COMT rs4860 polymorphism.

This meta-analysis has gathered all the available outcomes from the observation studies, which has dramtically increased the statistical power. However, there were several limitations which should be stated. First, there may be other factors, such as sex, age, weight, affecting the impacts of postoperation analgesia with opioid except COMT rs4860 gene polymorphism. In this meta-analysis, we only evaluated the effects of COMT rs4860 gene polymorphism on postoperation analgesia with opioid performance. Second, the number of current studies is not big enough. Thus, large sample size of diverse races needs studying for a more reliable evaluation on effects. Third, although the publication bias analysis did not show a statistical significance, a trivial potential study bias might have occurred in this meta-analysis. In addition, we did not consider researches published in languages except English or Chinese.

In conclusion, this meta-analysis suggested that the COMT rs4860 polymorphisms were associated with doses of opioid in 24 h after operation. COMT rs4860 gene may be useful to predict cases' response to postoperation anal-

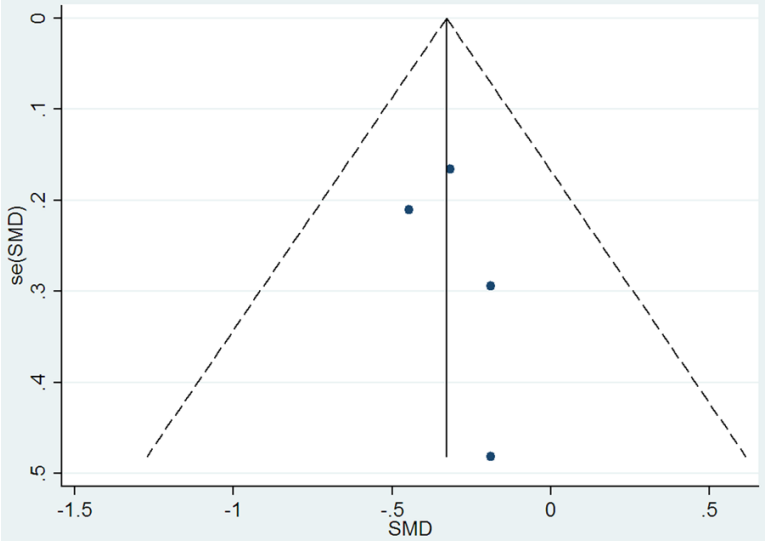

Figure 5. A funnel plot of effects of Catechol-O-Methyltransferase (COMT) rs4860 polymorphism on the opioid consumption for postoperation analgesia (AA vs. AG+GG).

gesia. However, this conclusion should be interpreted cautiously. To better understand the effects of COMT rs4860 polymorphism on postoperation analgesia with opioid in humans, large sample studies should be carried out in future.

Acknowledgements

Many thanks to Xiaomei Wu, Ph.D, Professor of the Department of Clinical Epidemiology and Evidence Medicine in the First Affiliated Hospital of China Medical University for her assistance in this work. This study was supported by Science and Technology Planning Project of Shenyang City (No. F13-221-9-71) and Liaoning Provincial Education Science and Planning Projects (No. JG14DB450) and Science and Technology Fund Project of Shenyang Medical College (No. 20142034).

Disclosure of conflict of interest

None.

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