The role of Factors in developing Acute and Chronic Pain following a Total Knee Arthroplasty

Stephen Sciberras[1,2], Bernice Vella[2], Adrian Vella[2], Jessica Antoinette Spiteri[2], Mizzi Christabel[2], Keith Borg Xuereb[2], Godfrey Laferla[1], Godfrey Grech[3]

1)Department of Surgery, University of Malta, Msida, Malta

2)Department of Anaesthesia, ITU and Pain Management, Mater Dei Hospital, Msida, Malta

3)Department of Pathology, University of Malta, Msida, Malta

INTRODUCTION

Total knee arthroplasty (TKA) is a common surgical procedure, and is associated with a significant amount of pain in the acute post-operative phase, but also after six months after surgery. Genetic variation might explain which patients are more prone to developing such chronic post-surgical pain (CPSP).

This study aims to investigate the role of 18 single nucleotide polymorphisms (SNP's) across six genes in the development of chronic pain after TKA: *COMT*, *SCN9A*, *KCNS1*, *OPRK1*, *OPRM1*, *GCH1.* (Figure 1)

METHOD

Patients aged 18 – 75 years who were to undergo a TKA were included in the study. Exclusion criteria included: rheumatoid arthritis, revision TKA, chronic pain conditions (eg fibromyalgia)

Genotyping

After enrolment, 3mL of blood was collected in an EDTA sample bottle. DNA was extracted using Qiagen® DNeasy Blood & Tissue Kits, to obtain a 50 µL sample, that was then checked for purity using a Nanodrop™ 2000 spectrophotometer (Thermo Fisher Scientific, US).

Various SNP's in different genes (Figure 1) were evaluated using Realtime PCR with TaqMan™ genotyping assays. Pre-validated allelic discrimination TaqMan real-time PCR assays were used for detection of such SNP's (Applied Biosystems, California, USA). Fluorescence data was captured using Roto-Gene Q (Qiagen GmbH, Dusseldorf, Germany), after 40 cycles of PCR.

Statistical Analysis

The primary outcome was pain at three and at six months as defined by the WOMAC® Pain subscore. Other outcomes measured were the incidence of CPSP, defined as a WOMAC® Pain subscore > 5, and the change in the WOMAC® Pain subscore from the pre-operative value.

RESULTS

In total, 200 patients were enrolled in the study. The overall incidence of chronic pain at six months was 11%, with only 37.5% of patients reporting no pain at all.

A number of SNP's investigated showed an effect on the outcome measures, as shown in Table 1.

Baseline pain scores were associated with rs2075572 (*OPRM1*), rs609148 (*OPRM1*).

There was no association between any of the genotypes and acute pain scores or opioid consumption.

The patients who developed CPSP were more likely to carry the rs563649 allele (*OPRM1*), the rs734784 allele (*KCNS1*) and the rs6985606 allele (*OPRK1*), as shown in Table 2.

Multivariate analysis of all SNP's showed:

- Preoperative pain was decreased with rs2075572 (*OPRM1*), and rs734784 (*KCNS1*)
- At 6 months, pain scores were increased in heterozygotes of rs11898284 (*SCN9A*), but decreased in carriers of rs6746030 (*SCN9A*)
- At 6 months, incidence of CPSP was increased with rs4633 (*COMT*), rs563649 (*OPRM1*), but reduced with rs734784 (*KCNS1*)

COMT
rs4633
rs4680
rs4818
SCN9A
rs6746030
rs7595255
rs11898284
OPRM1
rs1799971
rs2075572
rs495491
rs533586
rs609148
rs563649
GCH1
rs998259
rs3783641
KCNS1
rs4499491
rs734784
OPRK1
rs6985606

Figure 1: List of 18 Single Nucleotide Polymorphisms spread over 6 different genes that may be associated with pain syndromes

Gene	SNP	Baseline		3 months			6 months		
		WOMAC®	WOMAC® Pain	WOMAC®	WOMAC® Pain	Change in WOMAC® Pain	WOMAC®	WOMAC® Pain	Change in WOMAC® Pain
COMT	rs4633			↓				↓	↑
	rs4680								↑
	rs4818						↑	↑	↓
SCN9A	rs6746030								
	rs7595255								
	rs11898284				↓			↓	
OPRM1	rs1799971								↑
	rs2075572	↓	↓			↓			↓
	rs495491								
	rs533586								
	rs609148		↓						↑
	rs563649								
GCH1	rs998259								
	rs3783641								
KCNS1	rs4499491								↓
	rs734784	↓							
OPRK1	rs6985606								

Table 1: Summary of effect of different SNP's. Green: better outcome; Red: worse outcome. Wilcoxon sum rank test.

		CPSP	No CPSP	p-value
n		13	157	
COMT	rs4633 *	8 (62%)	113 (72%)	0.74
	rs4680	8 (62%)	113 (72%)	1.00
	rs4818	7 (54%)	87 (55%)	0.52
SCN9A	rs6746030	2 (15%)	45 (29%)	0.51
	rs7595255	3 (23%)	48 (31%)	1.00
	rs11898284	6 (46%)	38 (24%)	0.083
OPRM1	rs1799971	2 (15%)	44 (28%)	0.51
	rs495491	8 (62%)	84 (54%)	1 .00
	rs563649 *	5 (38%)	25 (16%)	***0.037***
	rs2075572	8 (62%)	109 (69%)	0.53
	rs533586	6 (46%)	93 (59%)	0.75
	rs609148	6 (46%)	68 (43%)	0.55
GCH1	rs3783641	3 (23%)	36 (23%)	0.73
	rs998259	5 (38%)	64 (41%)	0.74
KCNS1	rs4499491	7 (54%)	90 (57%)	1.00
	rs734784 *	5 (38%)	104 (66%)	0.088
OPRK1	rs6985606	10 (77%)	92 (59%)	***0.033***

*Table 2: Frequency of patients carrying minor allele in patients who developed CPSP. The SNP with * have been confirmed to be factors with multivariate analysis*

CONCLUSIONS

Genetic variations, especially in the *KCNS1*, *SCN9A*, *OPRM1*, *COMT* genes, and possibly in the *OPRK1* gene might predict the development of chronic pain at six months after a total knee replacement. Testing for variations in specific SNP's might help to direct more resources for patients at such a risk.

CONTACT INFORMATION

Dr Stephen Sciberras

stephen.sciberras@um.edu.mt