The Impact of Subclinical Depression on the Postoperative Perception of Pain in General Surgery Patients

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Abstract

Aim-Background: Postoperative pain is a significant cause of discomfort and interferes with the recovery and mobilization of surgical patients. Depression has been shown to sensitize patients to pain. We conducted this study in order to assess its effect on general surgery patients.

Materials and methods: We conducted a prospective study involving 400 consecutive patients who underwent general surgery. Various factors known to be associated with the perception of pain were recorded, including the level of depression as well as preoperative and postoperative pain for the first week. The psychological state was assessed using the *Hospital Anxiety and Depression Scale (HADS)*.

Results: According to the results obtained from the HADS, there were 323 patients who did not have high scores for depression and 63 who had a level of depression. Patients with depression were older, had a longer scar, scored high in the HADS for anxiety, depression, and had a lower level of education. They had greater preoperative pain and higher level of early postoperative pain (1st PO day). No difference was identified in the type and quantity of the analgesia used. Patients over 60 years of age and of lower education were mostly affected.

Conclusion: Subclinical depression is a significant predictor of pain. Measures should be taken to identify this subgroup of patients and manage them accordingly in order to minimize the effect on the perception of pain. We propose assessment of all surgical patients according to the HADS, special consultation of such patients, and medications to alleviate the psychological state.

Key words: *Anxiety*; *pain*; *determinants of pain*; *surgery*

Introduction

Any admission to the hospital, especially with the prospect of surgery, is extremely anxiety-provoking, resulting in behavioural and cognitive sequelae that can have a negative effect on the recovery of the patient [1]. In addition, postoperative pain is a significant cause of discomfort and interferes with the recovery and mobilization of surgical patients [2]. There is a bidirectional relationship between pain and psychological factors. Nonetheless, the mechanism by which depression and pain impact each other is not clear [3].

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Studies exploring the relationship between psychological factors and postoperative pain have predominantly focused on anxiety, leaving depression relatively unexplored [1].

Depression is a common psychological disorder, characterized by sadness, feelings of guilt or low self-worth, disturbed sleep or appetite, loss of interest or pleasure, feelings of tiredness, and poor concentration. It can be long-lasting or recurrent, impairing the person's ability to function at work or school or cope with daily life. In the majority of cases, depression can be diagnosed and managed adequately by non-specialists, leaving just a small proportion of individuals with complicated depression (major depressive disorder) or those who do not respond to first-line treatments given by specialists.

Pain is a subjective and multidimensional experience [4]. The IASP (International Association for the Study of Pain) defined pain as "an unpleasant sensory and *emotional experience* associated with actual or *potential* tissue damage, or described in terms of such damage" [5]. The association of tissue damage and pain is not always a direct one, and many people report pain in the absence of tissue damage or any likely pathophysiological cause [5]. Pain is often inad-equately managed in clinical practice. Nevertheless, effective

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control of postoperative pain is important after anaesthesia and surgery to prevent adverse sequelae caused by this.

A recent review of the literature showed that pain and depression impact each other and this has an important role in the development and maintenance of chronic problems. Accordingly, it is intriguing to understand this relationship in the special category of surgical patients. The interrelation of pain, distress, and depression is difficult to untangle because many studies are cross-sectional, prospective over short periods, or involve individuals who are already experiencing persistent pain [6]. Future studies of treatments for co-morbid depression and pain are required [3].

We conducted this prospective study in order to assess the interrelation of depression and pain in general surgery patients.

Materials and methods

The study was approved by the ethical committee of the hospital. Between September 2012 and February 2013, we prospectively enrolled 400 consecutive general surgery patients who fulfilled the inclusion criteria. Patients who could not comprehend well or who remained intubated after surgery were excluded from the study. At admission, they were asked if they wished to participate; if they agreed, they were interviewed by a trained doctor member of the study group. The interview was predesigned and based on the known factors related to postoperative pain. Apart from demographic questions concerning the educational level, other questions sought to establish the level of preoperative pain, use of analgesics or other medications related to pain or mood control, smoking history, previous experience of surgery, psychological state, type of surgery, and whether the operation was emergency or routine.

The psychological state was assessed with the Hospital Anxiety and Depression Scale (HADS) [7] which is a fourteen-item scale with a score ranging from 0–21 for each. A review on the validity and reliability of HADS confirmed the assumption that HADS performs well in screening for the separate dimensions of anxiety and depression [8]. Seven of the items relate to anxiety and seven to depression. It is a self-assessment scale for detecting symptoms of anxiety and depression in non-psychiatric patients from a medical department. Based on the score, we can classify the psychological status of the patients (anxiety, depression) as normal (0-7), mild (8-10), moderate (11-14), or severe (15-21). Scores for the entire scale (emotional distress) range from 0-42, with higher scores indicating more distress. For the purpose of the study, we then classified the patients into two groups: group A=normal (0-7) and group B=with a level of depression (>7).

Two methods were used to assess pain: (A) The visual

analogue scale (VAS) which is a psychometric response scale whereby the patient has to indicate a position along a continuous line between two end-points (no pain and maximum pain) [9] and (B) the *numeric rating scale (NRS)* which is a segmented numeric version of the visual analogue scale (VAS) in which the patient indicates the number (0–10) that best reflects the intensity of their pain. Both tests are easy to obtain, reliable, valid and can detect changes over time [9].

Pain intensity was assessed preoperatively and for the first seven postoperative days. The type and amount of analgesia required was also recorded from the 1st to the 7th postoperative day.

We purposefully did not record pain on the day of the operation, nor did we record the analgesia given since this depended greatly on the anaesthesiologist's preference. Nevertheless, from postoperative day one onwards, the analgesia given on demand from the patient was documented. The patients were given three options to assess the intensity of the pain, and were subsequently classified into three major groups: 1) NSAIDS (1-2/24h), 2) Tramadole HCL 50mg / pethidine 50mg (1-2/24h), and 3) Tramadole HCL 50mg / pethidine 50mg (>3/24h).

We further classified the patients into two groups: 1) NSAIDS, and 2) Stronger painkillers.

The educational level was classified as low for those whose education only reached junior school, and high for those who had attended senior school and above.

The operations were classified according to the type of incision into six categories: abdominal, laparoscopic, perianal, breast/skin, inguinal and others.

Statistics

The statistical analysis was carried out using SPSS for Windows version 17 software package (Statistical Package for Social sciences; Inc, Chicago, IL).

For categorical variables we used Pearson Chi-square test and Fisher's exact test.

For continuous variable we used an independent sample t-test for equality of means to assess if there were any statistically significant differences between the means of the outcome values.

For comparisons involving more than two groups we used analysis of variance (ANOVA) to identify statistically significant differences between the means of the outcome values of the groups.

Having rejected the Null hypothesis (i.e. statistically significant effect in ANOVA), we further applied follow-up tests (post hoc) to assess which groups were different from other groups or to test various other focused hypotheses. The "Tukey's" and "Bonferroni" post hoc tests were used. We considered significant differences as those with a p value less than 0.05. Binary logistic regression was used to assess if there were any significant predictors of binary outcomes.

Results

During the study period, 400 patients were enrolled, of whom 180 were male (45%) and 220 female (55%) with a mean age of 57.08 years. The vast majority of patients underwent a routine operation (88.3%). The mean weight was 75.42kg (41-132) and the mean height was 168.03 cm (120-190). The percentage of smokers was 35.3%, and 67% had experience of previous surgery. In terms of depression, 80.75% (group A) were classified as normal (no depression), and 15.75% (group B) had a level of depression. Patients of group A were younger than those in group B. Patients in group B also scored significantly higher for anxiety than those belonging to group A. The scar length was also longer in group B (table 1). Group B showed a female prevalence, and more people were of lower education level (table 2). Less people in group B used analgesics and narcotics before their admission to the hospital.

None of the patients was officially diagnosed with a depressive disorder, although as mentioned above some patients were under mild anxiolytic medication.

Patients in group B declared more preoperative pain than those in group A, although there was no difference in the percentage of urgent operations (p=0.069) or the type of operations between groups (p=0.390). Even when the operations were classified according to the type of incision used, there was no significant difference between groups (p=0.444). We found that patients in group B experienced significantly more pain on any given day than patients in group A, but the difference was significant only at the 1st PO day (table 1). Moreover, there was no difference between the two groups in the type or quantity of analgesia given (table2).

Since significant differences were noted in terms of gender, age, anxiety score, level of education and use of analgesics/narcotics, we proceeded with a multivariate analysis (logistic regression). The *anxiety score* (B=1.460, p<0.001) and the *level of education* (B=2.294, p=0.014) were

Table 1. Demographics and Outcomes.	Comparisons between group	A and group B for	quantitative variables.
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	No Depression	Depression	<u> </u>	
	group A	group B	Р	
Ν	323	63		
Age (SD)	55.65 (18.30)	63.49 (17.04)	0.002	
Weight (SD)	75.53 (15.52)	74.86 (14.62)	0.750	
Height (SD)	168.54 (9.33)	165.41 (7.96)	0.007	
Scar length	5.91 (4.20)	7.16 (6.09)	0.048	
Anxiety score	3.90 (3.22)	9.4 (3.99)	<0.001*	
Preop Pain NRS	1.86 (2.95)	3.22 (3.89)	0.002	
1 st PO NRS	3.31 (2.64)	4.43 (3.03)	0.003	
2 nd PO NRS	2.30 (2.43)	2.94 (2.65)	0.064	
3 rd PO NRS	1.58 (2.15)	2.08 (2.28)	0.094	
4 th PO NRS	1.08 (1.8)	1.35 (1.91)	0.287	
5 th PO NRS	0.77 (1.59)	0.98 (1.67)	0.340	
6 th PO NRS	0.57 (1.42)	0.83 (1.64)	0.210	
Preop Pain VAS	1.99 (3.06)	3.40 (3.64)	0.001	
1 st PO VAS	3.29 (2.71)	4.40 (3.08)	0.004	
2 nd PO VAS	2.30 (2.46)	2.94 (2.62)	0.062	
3 rd PO VAS	1.54 (2.11)	1.98 (2.25)	0.129	
4 th PO VAS	1.09 (1.82)	1.30 (1.89)	0.398	
5 th PO VAS	0.73 (1.59)	0.98 (1.68)	0.265	
6 th PO VAS	0.57 (1.41)	0.97 (1.63)	0.151	

SD = standard deviation, PO= post operative, VAS = visual assessment score, NRS= numerical rating scale

*From the confounding factors, the multivariate analysis showed that only differences in the anxiety level were significant.

	No Depression	Depression	X ²	р
	group A	group B		
Ν	323	63		
Gender (female)	51.8%	74.6%	11.098	<0.001
Education (low)	32.7%	54.7%	13.120	<0.001*
Use of narcotics	88.6%	63.5%	25.479	<0.001
Use of analgesics	83.1%	68.3%	7.506	0.007
Smoking	64.4%	63.5%	0.02	0.498
Previous Surgery	33.4%	28.6%	0.568	0.275
Urgent operation	9.9%	17.5%	3.038	0.069
Type of scar			4.773	0.444
Laparoscopic	29.2%	32.3%		
Abdominal	27%	25%		
Inguinal	13%	9.7%		
Breast/skin	16.8%	16.1%		
Perianal	4%	0%		
Other	10.2%	16.1%		
Anxiety				
yes	13.1%	66.7%	89.101	<0.001*
Analgesia				
Analgesia 1 st				0.856
Analgesia 2 nd				0.890
Analgesia 3 rd				0.345
Analgesia 4 th				0.325
Analgesia 5 th				0.300
Analgesia 6 th				0.310

Table 2. *Demographics and Outcomes. Comparisons between group A and group B for qualitative variables.*

*Analgesia (3 categories)= 1.NSAIDS (1-2/24h), 2.Tramadole HCL 100mg/pethidine 50mg (1-2/24h), 3.Tramadole HCL 100mg/pethidine 50mg (>3/24h). *From the confounding factors, the multivariate analysis showed that only differences in the level of education and presence of anxiety were significant.

found to be significant predictors of depression.

We performed a subgroup analysis based on the level of education (low vs. high):

Low education: We found that patients in group A (66.58 years) were younger than those belonging to group B (73 years), p=0.012. The scar was longer in group B (9.47 cm vs. 6.92, p=0.041). Group B had a higher anxiety score (9.26 vs. 4.05, p<0.001) than group A. There were no significant differences in height, weight, gender, use of analgesics/narcotics before the operation, smoking, previous operation, urgent operation, type of operation, and type of incision.

There were no differences in the level of the preoperative pain. Nevertheless, group B displayed more pain during the 1^{st} (4.47 vs 3, 23, p=0.027) and 2^{nd} PO day (3.71 vs 2.48,

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p=0.019), and this finding was observed both with the VAS and NRS. There were no significant differences thereafter. Despite the differences in pain intensity, there were no significant differences between the groups in terms of the type and quantity of analgesia required.

Higher education: Group B had a higher anxiety score (9.55 vs 3.83, p<0.001) than group A. There were no significant differences in the age, scar length, height, weight, gender, smoking, previous operation, urgent operation, type of operation, and type of incision.

There were more females in group B than in group A (79.3% vs. 50.9%, p=0.003) and more people used analgesics before the operation (41.4% vs. 16%, p=0.002). The same was true for the preoperative use of narcotics (51.7% vs.

9.6%, p<0.001). More patients suffered from anxiety in group B (69% vs. 12%, p<0.001).

There were significant differences in the level of preoperative pain since group B experienced more pain (3.48 vs. 1.89, p=0.022) and this finding was observed both with the VAS and NRS. There were no significant differences during the postoperative period. Finally, there were no significant differences between groups in terms of the type and quantity of analgesia required during the study period.

Subgroup analysis based on the anxiety status

No anxiety: Group B experienced more preoperative pain (3.71 vs. 1.72, p=0.047) and more pain during the 1st PO day (4.62 vs. 3.22, p=0.040). More patients in group B used analgesics before the operation (19% vs. 9.2% p=0.013) and more people had received a low level of education (57.1% vs. 32%, p=0.020). No other significant differences were found

Anxiety: No differences were observed in all the quantitative measures, including pain. More preoperative narcotics were recorded for group B (45.2% vs. 26. 6%, p=0.047). No other differences were noted in qualitative factors, including postoperative analgesia.

Despite the fact that age was not found to be significant in the multivariate analysis, given that it is a confounding factor and there were significant differences between the two groups, we carried out a further subgroup analysis.

Subgroup analysis based on the age group

A. Under 40 years of age

There were no significant differences in the age, scar length, height, weight, sex, smoking, level of education, previous operation, urgent operation, type of operation, and type of incision. Nevertheless, group B had a higher anxiety score (8.17 (SD=3.65) vs. 3.51(SD=2.74), p<0.025) than group A. The same was confirmed when we classified the patients according to the presence of anxiety. Group B had a higher anxiety percentage (50% vs. 8.1%, p<0.017) than group A. No other significant differences were observed between groups for the main outcomes (postoperative pain and analgesia).

B. 40-60 years of age

There were significant differences in the level of the preoperative pain since group B experienced more pain (3.47(SD=3.87) vs. 1.49(SD=2.62), p=0.038) and this finding was observed both with the VAS and NRS.

The mean anxiety score was higher in group B (9.95(SD=4.76)) than group A (4.10(SD=3.29)), p<0.01.

There were more females in group B than in group A (84.2% vs. 58.5\%, p=0.26) and more patients had anxiety in group B (78.7% vs. 14.2\%, p<0.001) than group A. No other significant differences were observed between groups for the main outcomes (postoperative pain and analgesia) and for other confounding factors.

C. Over 60 years of age

There were significant differences in the level of the pain during the first and second postoperative day. Group B experienced more pain (1st PO day 4.35(SD=2.86) vs. 3.13(SD=2.58), p=0.022 and 2nd PO day 3.46 (SD=2.95) vs. 2.35(SD=2.48), p=0.032). Nevertheless, the mean anxiety score was higher in group B (9.30(SD=3.71)) than in group A (3.91(SD=3.33), p=0.001).

Regarding the qualitative data, significant differences were noted in the gender, use of narcotics/analgesics, level of education, and degree of anxiety. In particular. a female predominance was observed in group B (75.7% vs. 47.9%, p=0.002), more patients in group B received analgesics/ narcotics (37.8% vs. 17%, p=0.008), more patients in group B were of lower education (75.7% vs. 52.1%, p=0.007) and finally, there were more patients with anxiety in group B (64.9% vs. 14.1%, p=0.001).

Discussion

Depression represents a very common co-morbidity of pain [10-12] and a significant predictor of postoperative pain [1,4,10,11]. It encompasses emotional and somatic symptoms which present in 30-54% of major depression disorders. Nevertheless, half of these cases are not diagnosed [5].

A meta-analysis found that 65% of depressed patients had pain-related symptoms [5,13]. This correlation is associated with a poor quality of life, increased postoperative functional disability, decreased work function, loss of productivity, increased co-morbidities, transient suppression of the immune system, poor recovery, higher mortality, increased health care utilization and costs [1,4,6,10,14.15].

Depression represents a risk factor for the progression of acute pain to chronic pain [10,16,17]. Forty per cent of all emergency department (ED) visits for pain are due to chronic pain [15]. Fifty per cent of patients with persistent pain have significant depression [17]. One-third of ED patients are diagnosed with depression, but frequently remain undiagnosed and untreated due to pain [15].

Depression is associated with the development of chronic pain as well as with poor treatment results. Two possible mechanisms may explain the link between depression and pain. First, "catastrophizing" plays a central role in models of both pain and depression and hence might represent an important link between them. Second, emotion regulation is important in both depression and pain since they can both be viewed as significant emotional stressors. A model which focuses on the recurrent nature of pain and depression hypothesizes that flare-ups trigger catastrophic worry which in turn strains the individual's emotional regulation system. It seems that managing to successfully regulate emotion facilitates coping, while failure to do so has a negative effect, leading to pain and mood-related disability and, in the long term, a consequent relapse. It is obvious that this close association between pain and depression leads to the development of long-term problems, and it is important that clinicians assess them as early as possible. Moreover, both conditions should be monitored and addressed during treatment to improve outcome results; a combination of medical and cognitive-behavioural therapy may be necessary [3]. Surgery by definition is a significant cause of pain. Moreover, patients waiting to be operated on suffer from emotional distress at varying degrees that leads to anxiety and/or depression, which in turn affects the perception of pain.

While depression is typically seen to trigger pain and lead to chronicity, whether depression is the cause or the result of pain is still under debate [12]. The fact is that the association between depression and pain is bidirectional with each disorder preceding the other. Patients with depression are at increased risk for pain and patients with pain at increased risk for depression. It is difficult to determine whether pain precedes and predicts depression or whether depression is an antecedent of pain [1,6,10,13,15,16].

The present study included 180 males and 220 females (total 400 patients), the majority of whom underwent elective surgery (88.3%), including laparoscopic cholecystectomies and appendicectomies, open HPB operations, colorectal surgery, incisional and inguinal hernias, breast surgery, thyroidectomies and varicose veins. We attempted to analyze the correlation of depression with postoperative pain in these general surgery patients, although various confounding factors were involved. Just under one-third of the patients in our series were diagnosed as cases presenting a level of subclinical depression.

Depression has been shown to be a predictor of pain in various other medical conditions. In a multicentre, cross-sectional study consisting of 3,566 patients attending psychiatric clinics, a high occurrence of chronic pain was found among patients with major depression (43,4%) and a longer depression episode in those experiencing pain. Furthermore, 43% of depressive patients had no apparent cause of pain or nociceptive stimulus [6]. In a systematic review of 48 articles, involving 23,037 patients, depression was found to be a significant predictor of postoperative pain. Among six studies concerning the correlation of depression and postoperative pain, four found a positive correlation and two no correlation. In three studies concerning the correlation of depression and postoperative analgesic requirements, two found positive correlation and one no correlation [4]. In another study consisting of 82 patients undergoing elective laparoscopic cholecystectomy, it was found that depressed patients experienced more severe pain and required extra tramadol in comparison to non-depressed patients. The peak of analgesic consumption was at the 8th postoperative hour [18]. Among a total of 16 prospective studies on the impact of depression, 14 reported a significant relationship. Six investigations looked at depression in samples of people from a workplace or the general public. Five studies demonstrated a relationship with the future onset of pain but in three of these samples, participants declared previous or current pain at the pretest measurement. Furthermore, one study found that the increased risk was moderate. Finally, one study did not find a relationship [12]. Nevertheless, to our knowledge, there is not a single study where the impact of depression on the postoperative pain was studied in general surgery patients. Moreover, in our prospective study we included all the known predictors of postoperative pain in order to avoid bias caused by other confounding factors.

Even though a clear link between depression and pain has been established, little is currently known about the mechanism by which they interact [12]. Rather than a trigger, it might be more accurate to view depression as a force that catalyzes pain problems. When depression is present during the early stages of pain, it is clearly linked to a higher probability of the development of longstanding pain problems [12].

In our study, we initially noticed that depressed patients were older, they had a higher anxiety score, the majority were females and they had received a lower level of education. Since there were significant differences between gender, age, anxiety, level of education and use of analgesic and narcotics, we performed a multivariate analysis and found that only anxiety and level of education were significant predictors of depression.

According to the subgroup analysis based on the level of education, we found that patients of low education level had identical results with the overall results. Conversely, patients with higher education presented no significant differences regarding pain during the postoperative period. This is in line with other similar studies where patients of lower education and with heart failure experienced more pain than those of higher education level during the first six months [19]. A study investigating the association of educational level and mood disorders in more than 10,000 people from the general population showed that the relative risk for anxiety was significantly higher in persons of lower education and this was more pronounced in females. Moreover, the same was true for depression where it was found that the lower the education level, the higher the relative risk [20]. Studies have shown that there is a cumulative protective effect of high education on mood disorders, especially depression, and a subsequent advantage on physical health [21]. It has been shown that gaining control or understanding better the anticipated condition leads to better adaptation and improved tolerance of it since the condition may prove less threatening [22]. This can be achieved by proper education of the patients and depends on the level of education and the way the medical staff approaches the patients. Educating the patients on the medical action to be taken should not be a passive process with no confirmation of whether the information is understood. On the contrary, it should be an interactive process, with confirmation that it has been understood [22]. Based on this, we may assume that patients of lower education cannot handle their subclinical depression well during the perioperative period as opposed to those with higher education. The first conclusion of this study was that depression may indeed lead to greater postoperative pain, but this applies to the subgroup of patients with lower education.

Hence, the level of education should always be taken into account during the preoperative assessment of the patient. If the patients are of lower education, they should be further assessed for depression and anxiety (e.g. with the *Hospital Anxiety and Depression Scale (HADS)*) and if found not to be entirely normal, special effort and extra care should be given in educating them properly to alleviate their psychological distress. If we succeed, we will probably manage to compensate for their "handicap", minimize the impact of lower education on postoperative pain, and allow them to have a better, more comfortable and less stressful recovery from the operation. Further RCTs are warranted in order to provide more evidence concerning the success of this approach.

Regarding the subgroup analysis based on the anxiety status, we found that in the subgroup of patients without anxiety, those with depression experienced more preoperative pain (3.71 vs. 1.72, p=0.047) and more pain during the 1st PO day (4.62 vs. 3.22, p=0.040), while in the subgroup of patients with anxiety there were no differences in all the quantitative measures including pain. This is important because a significant predictor of pain, such as anxiety which is also closely linked to depression, was excluded as a confounding factor. The fact that in the subgroup of patients without anxiety the impact of depression was significant means that depression is indeed an independent predictor of pain. This is also important since patients presenting in the emergency department with pain are highly likely to present anxiety (two-thirds display a level of anxiety) [24] but this does not mean it is the only emotional factor to be taken into account.

Despite the results of the multivariate analysis, we further stratified the patients into three age groups: under 40, 40-60 and over 60 years of age. Interestingly, we found that only in the subgroup of patients who were older than 60 did depression actually affect postoperative pain.

Based on our findings, apart from recognizing and dealing with anxiety, depression was found to be an independent predictor of pain and there is a need to treat both depression and pain in order to maximize outcome results and provide better postoperative recovery.

We identified which categories of surgical patients are at higher risk of experiencing more pronounced pain because of the effect of depression. Such patients include those of lower education status and those aged over 60 years.

In conclusion, depression is an independent predictor of pain in general surgery patient, having a greater effect on older patients and those with lower education. These patients should at least be assessed for subclinical depression and measures should be taken to deal with it preoperatively in order to minimize the postoperative effect on pain and the consequent associated complications.

Ethical Approval - Informed Consent

The authors declare that the study has been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Also all patients gave their written informed consent prior to their inclusion in the study for publication of their personal data.

Conflict of Interest

The authors declare that there is no conflict of interest.

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