UNIVERSIDADE DA BEIRA INTERIOR
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Gestão da medicação crónica no período perioperatório
Avaliação das recomendações terapêuticas baseadas na evidência

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Dedicatória

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Resumo

Introdução: Atualmente, um número crescente de cirurgias é realizado em populações cada vez mais idosas o que poderá representar um maior risco de complicações, quer devido à comorbilidade inerente, quer à polimedicação associada. A instituição de medicação crónica nestes doentes permite que estes tenham as suas doenças crónicas estabilizadas, o que possibilita a realização de uma cirurgia. Por outro lado, a evolução das técnicas cirúrgica e anestésica, permite o aumento da acessibilidade aos cuidados cirúrgicos, bem como o recurso crescente a intervenções complexas. Assim, é da maior pertinência atual avaliar as consequências da gestão da medicação crónica no período perioperatório. O estudo realizado em 2000 por Kennedy e colaboradores identificou que 49% dos doentes submetidos a cirurgia geral ou vascular tomavam medicação crónica, e que esta estava associada a um risco relativo de 2.7 de complicações no pós-operatório, comparativamente aos doentes sem qualquer medicação. Ainda neste estudo, verificou-se que 5% dos doentes que tomavam medicação tiveram complicações diretamente relacionadas com a suspensão dessa medicação no período perioperatório. Na literatura publicada são escassos os dados sobre a utilização e gestão da medicação crónica nos doentes cirúrgicos, durante o período perioperatório. Adicionalmente, são poucos os estudos que avaliam o risco de acontecimentos adversos associados à suspensão versus continuação da medicação crónica no mesmo período.

Objetivos: Os objetivos principais da presente dissertação são: (1) definir normas de orientação clínica baseadas na evidência para a gestão do risco iatrogénico no período perioperatório e (2) caracterizar e avaliar a gestão da medicação crónica no período perioperatório.

Material e Métodos: (1) As normas de orientação clínica foram definidas através da realização de uma revisão sistemática e de um consenso formal. A revisão sistemática consistiu na pesquisa de literatura nas bases de dados *Medline, Embase, ISI Web of Knowledge* e na *Medscape*. Dois investigadores independentes avaliaram a qualidade dos estudos selecionados utilizando os níveis de evidência da *Scottish Intercollegiate Guidelines Network*. Na pesquisa bibliográfica verificou-se que existiam normas de orientação clínica publicadas com classificação do grau de recomendação, para determinados grupos terapêuticos, designadamente os bloqueadores betas, as estatinas e os antitrombóticos. Assim, foi decidido não integrar estes grupos terapêuticos no consenso formal. O consenso formal foi realizado tendo como base uma técnica de grupo nominal modificada. Definiram-se 32 recomendações com base na revisão sistemática previamente realizada. Estas recomendações foram estruturadas num formulário, com o objetivo do painel de especialistas pontuar cada uma segundo o respetivo grau de concordância. O painel era constituído por sete especialistas com

experiência reconhecida em medicina interna, medicina baseada na evidência, cirurgia geral, anestesiologia e farmácia. A primeira avaliação foi realizada por correio eletrónico. Numa segunda fase, foi realizada uma reunião, em que cada recomendação foi discutida e por fim, foi feita novamente uma avaliação das recomendações por correio eletrónico. As recomendações que obtiveram consenso entre os especialistas foram definidas como normas de orientação clínica. (2) Para a caracterização e avaliação da gestão da medicação crónica no período perioperatório realizou-se um estudo coorte retrospetivo no Centro Hospitalar Cova da Beira. Os doentes foram selecionados na consulta de anestesia, entre Setembro de 2008 e Setembro de 2009. O doente foi entrevistado antes da consulta de anestesia, para garantir que cumpria os critérios de inclusão. Os outros dados (dados demográficos, utilização de medicação crónica, informação clínica e acontecimentos adversos) foram recolhidos do processo clínico cirúrgico e do relatório dos episódios de urgência do programa informático ALERT®.

Resultados: A revisão sistemática selecionou e classificou o nível de evidência de 23 estudos: 3 ensaios clínicos randomizados, 13 estudos coorte, 3 caso-controlo e 3 casos clínicos. O consenso formal definiu 22 normas de orientação clínica para a gestão da medicação crónica no período perioperatório. No estudo coorte foram incluídos 929 doentes submetidos a cirurgia eletiva entre Setembro de 2008 e Julho de 2010. Verificou-se que 71.3% dos doentes cirúrgicos tomavam medicação crónica, numa média de 2.4 medicamentos por doente. Dos doentes que tomavam medicação crónica, 62.1% faziam terapêutica para o sistema cardiovascular. Independentemente do grupo terapêutico, 89.9% dos doentes suspendeu a medicação crónica no período perioperatório. Na análise efetuada, ajustada para as variáveis de confundimento, verificou-se, para esta população, que tomar medicação crónica e suspender a respetiva medicação no período perioperatório não são fatores de risco para a ocorrência de acontecimentos adversos.

Conclusões: O consenso formal mostrou ser um método prático e útil que permite integrar diferentes formas de evidência para o desenvolvimento de normas de orientação clínica. No estudo realizado verificou-se que a toma de medicação crónica e a sua gestão no período perioperatório (suspensão/continuação) não aumenta o risco de acontecimentos adversos no mesmo. Esta evidência deve ser analisada com cautela dadas as limitações do estudo assinaladas.

Palavras-chave

Medicação crónica, período perioperatório, acontecimentos adversos.

Abstract

Introduction: A large number of surgical procedures is daily performed worldwide. These interventions are performed in an progressively elderly population. Since many of these patients have multiple pathologies and receive chronic medication, this population is at an increased risk of surgery associated complications. Nevertheless, It has become increasingly possible to perform surgery in this population because chronic medication improves their general health status and major advances in anaesthetic and surgical techniques have occurred. Surgery and chronic medication management should be consistently evaluated. Kennedy and colleagues found that 49% of the general surgical patients take medications unrelated to surgery and that was associated with a postoperative complication relative risk of increased of 2.7, when compared with those not taking any medication. The same study show that, 5% of the patients suffered postoperative complications directly attributable to chronic medication withdrawal. Unfortunately, there is limited outcome data about the most frequent chronic medications therapeutic groups taken in the perioperative period and how clinicians should manage them. Also, there is a lack of evidence quantifying the risk of adverse events associate with chronic medication suspension versus continuation during the perioperative period.

Objectives: (1) to develop evidence based recommendations for the management of chronic medication in the perioperative period; (2) to evaluate chronic medication use in a surgical population and the impact of its management in the incidence of perioperative adverse events.

Material and Methods: (1) A systematic review and a formal consensus were performed to definition of guidelines. A search in Medline, Embase, ISI Web of Knowledge and Medscape were conducted. The quality of selected studies was evaluated by two independent investigators using the Scottish Intercollegiate Guidelines Network levels of evidence. Evidence-based guidelines were found for some therapeutic groups, namely ß-blockers, statins and antithrombotic therapy. Those guidelines were adopted and no further analysis was done. For other therapeutic groups, a formal consensus was used, based on a modified nominal group technique: 32 statements were formulated considering the literature retrieved. A selected panel of experts was asked by electronic mail to rate their level of agreement with each statement. This panel comprises seven specialists with recognized expertise in internal medicine, evidence-based medicine, surgery, anaesthesiology and pharmacy.Then, a meeting was convened and a second round survey was used to determine the final level of agreement. The statements which met the established criteria of consensus were developed into practice recommendations.

(2) An retrospective study was carried in *Centro Hospitalar Cova da Beira* to: a) identify the chronic medication use profiles of a surgical population; b) quantify the relative importance of taking chronic medication and its impact on perioperative management and the incidence of adverse events. Patients attending the *Centro Hospitalar Cova da Beira* clinics were recruited between September 2008 and September 2009, at. Patients were interviewed before anaesthesia consultation by a member of the research team to ensure that enrollment criteria were met. All other data (demographic characteristics, chronic medication use, the clinical information and adverse events) were gathered from postoperative review of medical records and from the ALERT® report of urgency episodes.

Results: (1) A total of 23 studies were included in the systematic review - 3 randomised controlled trials, 13 cohort studies, 2 case-controls studies and 3 clinic-cases. Twenty two chronic medication management practice recommendations in the perioperative period resulted from formal consensus. (2) The study included 929 patients submitted to elective surgery during the study period. A total of 71.3% of patients were on chronic medication. The mean number of drugs taken was 2.4 ± 2.5(1-14). Of the patients taking chronic medication, 62.1% were on drugs for cardiovascular system and 89.9% did withdraw it during perioperative period. The analysis performed, after adjusting for confounding variables, reveal that both taking chronic medication and withdrawal were not risk factors for the occurrence of adverse events.

Conclusions: The formal consensus method proved to be a helpful tool to integrate different evidence documents for the development of practice guidelines. This work also provides limited evidence that chronic medication and its management, either continuing or the withdrawal of it, may not add significant risk to perioperative period. Due to the study limitations discussed, these results must be considered with caution.

Keywords

Chronic medication, perioperative period, adverse event.

Índice

Lista de Acrónimos

AA	Acontecimentos Adversos
ASA	*American Society of Anesthesiology*
AINES	Anti-inflamatórios não esteróides
CHCB	Centro Hospitalar Cova da Beira
IC	Intervalo de confiança
MERA	Modificadores do eixo renina e angiotensina
NOC	Normas de orientação clínica
THS	Terapêutica hormonal de substituição
UBI	Universidade da Beira Interior

Capítulo 1

Introdução

Atualmente, um número crescente de intervenções cirúrgicas é realizado em populações cada vez mais idosas o que representa um maior risco de complicações, quer devido à comorbilidade inerente, quer à polimedicação associada (Weiser *et al*. 2008). A instituição de medicação crónica permite que estes doentes tenham as suas doenças crónicas estabilizadas, de forma a poderem realizar uma cirurgia. Por outro lado, a evolução das técnicas cirúrgica e anestésica, possibilita o aumento da acessibilidade a cuidados cirúrgicos, bem como o recurso crescente a intervenções complexas.

1.1 A Medicação Crónica e o Período Perioperatório

Em Portugal, no ano de 2009, foram realizadas 475293 cirurgias programadas, das quais 55.3% implicaram internamento (ACSS 2010). Num relatório efetuado em 2008, a média de idade dos utentes operados em Portugal era de 54 anos, contudo a maioria tinha idade compreendida entre os 60 aos 80 anos (Cristovão R. 2008). Num estudo realizado no norte de Portugal, entre 2005 e 2006, verificou-se que a prevalência do consumo de medicação crónica foi de 58,1%, sendo que os grupos etários dos 56 aos 65, dos 66 aos 75 e com mais de 75 anos apresentavam uma prevalência de consumo de medicação crónica de 80.3%, 91.3% e 91.1%, respetivamente (Cima *et al*. 2011). Estes dados indicam que a toma de medicação crónica é um fator presente na vasta maioria dos doentes submetidos a cirurgia, em Portugal.

Em 1984, num estudo prospetivo verificou-se que 24 a 32% dos doentes cirúrgicos tomavam medicação crónica, sendo que 10 a 16% destes faziam terapêutica cardiovascular. Relativamente ao último grupo, a 29% dos doentes não foi prescrita terapêutica no pré-operatório e 59% não receberam a respetiva medicação no dia da cirurgia (Duthie *et al*. 1987).

Wyld e Nimmo verificaram que 42% dos doentes cirúrgicos tomavam medicação crónica, e que 29% desta não foi administrada quer no dia da cirurgia quer no dia seguinte (Wyld *et al*. 1988).

Num estudo publicado em 1991, identificou-se que 44% dos doentes cirúrgicos tomavam medicação crónica, sendo que 41% dos fármacos eram para problemas cardiovasculares (Kluger *et al*. 1991).

Kennedy *et al*, publicou no ano 2000 um estudo observacional e prospetivo, o qual identificou que 49% dos doentes submetidos a cirurgia geral ou vascular tomavam medicação crónica. Cada doente tomava em média 2.4 medicamentos, sendo que este número aumentava com a idade. É de referir que 48% destes doentes tomavam medicação crónica para problemas cardiovasculares, sendo que 90% tomavam 2 ou mais fármacos desta classe terapêutica. Adicionalmente, 45% dos doentes faziam medicação para o sistema nervoso central. Neste mesmo estudo, verificou-se que 23% dos doentes tiveram complicações, tendo sido determinado que os fatores de risco para qualquer complicação clínica, por ordem de importância, foram: a duração da cirurgia, a toma de medicação para problemas cardiovasculares ou para o sistema nervoso central, a permanência por mais de 24 horas no pós-operatório sem fazer a medicação crónica por via oral e a idade do doente. Assim, neste estudo concluiu-se que a toma de medicação crónica estava associada a um risco acrescido de 2.7 (95% IC 1.76-4.04) de complicações pós-cirúrgicas, das quais 5% foram diretamente atribuídas à suspensão da medicação. A toma de terapêutica cardiovascular contribuía significativamente para este risco, pois, quando excluída da análise, o risco diminuía para 1.8 (95% IC 1.14-2.93) (Kennedy *et al*. 2000).

Em 2001, os resultados de um estudo caso-controlo permitiram concluir que a toma de medicação crónica não aumenta o risco de morte cardíaca no pós-operatório, contudo é evidenciado que os nitratos poderão ser uma exceção (Sear *et al*. 2001).

Para além dos estudos descritos acima, existem ainda estudos e descrição de casos clínicos que identificaram as consequências da suspensão e da continuação da toma de determinados fármacos no período perioperatório, nomeadamente os bloqueadores beta, os modificadores do eixo renina angiotensina, as estatinas e os antidepressivos tricíclicos (Brabant *et al*. 1999; Pigott *et al*. 1999; Barber *et al*. 2001; Bertrand *et al*. 2001; Shammash *et al*. 2001; Comfere *et al*. 2005; Schouten *et al*. 2007).

Relativamente à realidade portuguesa, apesar da exaustiva pesquisa bibliográfica efetuada, não foi possível localizar publicações que quantifiquem o número de doentes submetidos a cirurgia a tomarem medicação crónica, que identifiquem os grupos terapêuticos mais prevalentes ou que avaliem a gestão da medicação crónica no período perioperatório.

Outros fatores a considerar na gestão da medicação crónica no período perioperatório são os efeitos da cirurgia na absorção dos fármacos, assim como as consequências do *stress* cirúrgico.

A medicação crónica é geralmente administrada oralmente, contudo a cirurgia e os seus efeitos podem comprometer a utilização desta via (Aitkenhead 1988; Elfant *et al*. 1995; Hackam *et al*. 1998). Durante a anestesia geral, os doentes estão em risco de aspirar o conteúdo gástrico. Assim, desde 1946, (Mendelson 1946) recomenda-se que os doentes "não podem comer nem beber desde a meia-noite do dia anterior à cirurgia". Contudo, como os

líquidos são eliminados do estômago duas horas após a sua ingestão, os doentes que ingerem líquidos límpidos antes da cirurgia não apresentam um conteúdo gástrico com maior volume e acidez que os doentes que estão em jejum completo em média 9 horas (Bateman *et al*. 1982; Phillips *et al*. 1993). Assim, é permitido ao doente tomar a sua medicação crónica até 2 horas antes da administração da anestesia. Vários fatores podem inibir o esvaziamento gástrico no doente no pós-operatório: a própria cirurgia, a administração de analgésicos opióides ou de catecolaminas e o comprometimento da capacidade de absorção do intestino (Singh *et al*. 1994; Dive *et al*. 2000; Fruhwald *et al*. 2002).

A cirurgia é um procedimento que interfere com as respostas neuroendócrina e metabólica, nomeadamente pela ativação do eixo hipotálamo-hipófise-glândula adrenal e do sistema renina-angiotensina, bem como pelo aumento da hormona anti-diurética, das catecolaminas e das citocinas (Weissman 1990; Naito *et al*. 1992; Desborough 2000).

Face a esta realidade, é fundamental identificar os perfis de utilização de medicação crónica no doente cirúrgico, obtendo assim um melhor conhecimento do risco de acontecimentos adversos associados ao regime de terapêutica crónica instituído no período perioperatório. A gestão do risco iatrogénico inerente a cada opção terapêutica deve ponderar de forma integrada a possibilidade de exacerbação dos sintomas da patologia de base desencadeada quer por síndrome de abstinência, quer por aumento da susceptibilidade a complicações patológicas resultante das alterações fisiológicas inerentes ao ambiente cirúrgico, quer, ainda, por eventual compromisso da efetividade terapêutica por interação com a medicação anestésica ou por alterações farmacocinéticas durante a cirurgia.

É de referir que as possíveis complicações associadas à continuação/suspensão da medicação crónica não dependem exclusivamente do fármaco em questão, mas também da gravidade da patologia para qual o fármaco está indicado, do grau de controlo alcançado com a terapêutica, assim como da presença de outras patologias de base, do procedimento cirúrgico e da técnica anestésica. Desta forma, é fundamental dispor de informação clínica e farmacológica exaustiva que permita uma avaliação individualizada da relação benefício/risco, procedendo, sistematicamente, ao respetivo registo.

1.2 Normas de Orientação Clínica para a Gestão da Medicação Crónica no Período Perioperatório

Atualmente, é reconhecido que as normas de orientação clínica (NOC) são fundamentais para a melhoria da prática clínica, permitindo a garantia de uma maior segurança para o doente. A evidência científica do impacto da gestão da medicação crónica no período perioperatório é limitada. Desta forma, as NOC publicadas são suportadas principalmente por consenso de especialistas, análise de casos clínicos, recomendações da indústria farmacêutica e outros

dados disponíveis (farmacocinética, interações com anestésicos, etc) (Mercado *et al*. 2003; Roig 2004; Saber 2006; Muluk *et al*. 2008). Relativamente à gestão da medicação crónica no período perioperatório em Portugal, não foi identificada nenhuma publicação de NOC.

Capítulo 2

Objetivos e Organização Geral da Dissertação

Os objetivos principais da presente dissertação são:

1) Definição de NOC baseadas na evidência para a gestão do risco iatrogénico no período perioperatório;

2) Caracterização e avaliação da gestão da medicação crónica no período perioperatório

    a. Identificação do perfil de utilização de medicação crónica pelo doente cirúrgico no período perioperatório;

    b. Quantificação do risco relativo de acontecimentos adversos no período perioperatório associados à toma de medicação crónica pelo doente cirúrgico;

    c. Quantificação do risco relativo de acontecimentos adversos no período perioperatório associados à gestão da medicação crónica no período perioperatório;

    d. Identificação de grupos terapêuticos associados a um maior risco de acontecimentos adversos no período perioperatório;

    e. Análise da aplicação das NOC baseadas na evidência para a gestão da medicação crónica no período perioperatório.

Desta forma, no âmbito dos objetivos definidos, realizaram-se os seguintes procedimentos:

1) Revisão sistemática de estudos e NOC publicadas na literatura internacional sobre a gestão da medicação crónica no período perioperatório;

2) Realização de um consenso de especialistas para a definição de NOC para a gestão da medicação crónica no período perioperatório, em Portugal;

3) Estudo coorte retrospetivo que incluiu os doentes presentes na consulta de anestesia do CHCB, entre Setembro de 2008 e Setembro de 2009, com cirurgia de internamento programada das especialidades cirúrgicas, nomeadamente, cirurgia geral, ortopedia, ginecologia, maxilo-facial, cirurgia plástica, urologia e neurologia.

A metodologia seguida nos procedimentos acima referidos encontra-se descrita nos artigos apresentados no capítulo 4.

No decurso da evolução do trabalho desenvolvido revelou-se indispensável proceder a alterações significativas da metodologia inicialmente prevista. Assim, no capítulo 3 são discutidas as opções metodológicas efetuadas.

No capítulo 5 é efetuada a discussão das principais questões abordadas nos artigos publicados e submetidos.

No capítulo 6 são apresentadas as conclusões gerais do trabalho efetuado, recomendações e perspetivas para o futuro.

Capítulo 3

Opções Metodológicas

Na proposta inicial do plano de trabalho para obtenção do grau de Doutor em Biomedicina, o objetivo era realizar um estudo prospetivo com a duração de 12 meses, o que permitiria incluir aproximadamente 1000 doentes. O primeiro passo consistia na seleção dos doentes que preenchiam os critérios de inclusão (ver página 52, capítulo 4, os métodos do artigo 4.2.2) antes do início da consulta de anestesia, momento em que o estudo era apresentado aos doentes e solicitado o consentimento informado. A colheita dos dados seria feita em 5 momentos através do preenchimento de um formulário pelo investigador:

I. Antes da consulta da anestesia (consentimento informado),
II. Na consulta de anestesia,
III. No dia da cirurgia,
IV. Três dias após a cirurgia,
V. No dia da alta clínica.

Nestes 3 últimos momentos previa-se que o investigador acompanharia a visita clínica do médico. Esta metodologia implicava a colaboração do médico para a validação de eventuais "acontecimentos adversos". Após ter sido aprovado pela comissão de ética do CHCB, EPE, o estudo foi apresentado à diretora do Serviço de Anestesia que manifestou a sua disponibilidade e interesse em participar.

Nesta fase foi possível constatar que alguns médicos não queriam a presença do investigador na consulta. Assim decidiu-se abordar os doentes antes da consulta e analisar os registos efetuados pelo anestesista nomeadamente o formulário que o clínico deve preencher no decorrer da consulta.

Subsequentemente o estudo foi apresentado ao diretor do Departamento de Cirurgia. Após esta reunião, concluiu-se que do ponto de vista organizativo era dificilmente viável estar presente em todas as visitas clínicas, pois a autora era a única investigadora a realizar a parte prática do estudo. Para que tal se concretizasse 12 meses não seriam suficientes para obter o número de doentes inicialmente previsto. Por outro lado, revelou-se impossível contar com a colaboração e disponibilidade da maioria dos médicos. Assim, optou-se por fazer o seguimento do doente através da consulta do processo clínico informático uma vez que da análise de alguns processos clínicos da cirurgia (em formato de papel) e da orientação recebida do pessoal de enfermagem seria o processo informático o mais completo.

Todavia, para tal se concretizar era indispensável obter a respetiva autorização de acesso a qual viria a ser recusada pela Direção, do Centro Hospitalar Cova da Beira (CHCB) do ano 2008. Inicialmente a justificação apresentada foi a de que apenas os médicos e os enfermeiros podiam ter acesso aos programas respetivos. Após a nossa insistência para que fosse permitido um acesso restrito (apenas consulta sem qualquer tipo de modificação de dados) foi alegado que, por questões éticas, não seria possível consultar os referidos registos, apesar do estudo já ter a aprovação da Comissão de Ética do CHCB.

Assim, como alternativa, solicitou-se uma autorização para consulta dos processos clínicos escritos, a qual foi concedida.

Como se depreende, perante estas adversidades, o estudo inicialmente previsto teve que ser adaptado às condições disponibilizadas pelo CHCB.

Capítulo 4

4.1 Artigos Publicados

4.1.1 Artigo I

Castanheira L, Fresco P, Macedo AF. **Guidelines for the management of chronic medication in the perioperative period: systematic review and formal consensus.** J Clin Pharm Ther. 2011 Aug;36(4):446-67. doi: 10.1111/j.1365-2710.2010.01202.x. Epub 2010 Oct 26. PMID: 21729111

4.1.2 Artigo II

Castanheira L, Palmeiro A, Fresco P, Macedo AF. **A medicação crónica no período perioperatório. Perfil de utilização e gestão de risco.** Acta Med Port. 2011 Nov; 24(6):893-8. Epub 2012 Feb 20. Portuguese. PMID: 22713182

4.2 Artigo Aceites para Publicação

4.2.1 Artigo III

Castanheira L, Castro ML, Calheiros J. **Chronic utilization of agents acting on the renin-angiotensin system and intraoperative arterial pressure**. Eur Rev Med Pharmacol Sci. Aceite para publicação dia 25 Julho 2012.

4.2.2 Artigo IV

Castanheira L, Castro ML, Calheiros J. **Perioperative Chronic Medication Management.** Lat Am J of Pharm. Aceite para publicação dia 18 de Agosto de 2012.

4.1.1 Artigo I

"Guidelines for the management of chronic medication in the perioperative period: systematic review and formal consensus"

Liliana Castanheira, Paula Fresco, Ana Filipa Macedo

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REVIEW ARTICLE

Guidelines for the management of chronic medication in the perioperative period: systematic review and formal consensus

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SUMMARY

What is known and Objective: **The worldwide volume of surgery is huge and the number of interventions performed is increasing as a result of advances in technological resources and refinement of medical teams' expertise, in a progressively elderly and sick population. Consequently, half of the general surgical patients take medications unrelated to surgery. Evidence-based guidelines for perioperative medication management are therefore critically needed to improve safety in surgery. The purpose of this work was to develop practice recommendations for the management of chronic medication in the perioperative period.**

Methods: **A systematic review and a formal consensus were performed. A search in Medline, Embase, ISI Web of Knowledge and Medscape were conducted in September 2008. Two independent investigators assessed the quality of selected studies. Evidence-based guidelines with strength classification were found for some therapeutic groups. Those guidelines were adopted and no further analysis was performed. For the other therapeutic groups, a formal consensus was used, based on a modified nominal group technique: 32 statements were formulated considering the literature retrieved. A selected panel of experts was asked by electronic mail to rate their level of agreement with each statement. Then, a meeting was convened and a second round survey was used to determine the final level of agreement. The statements which met the established criteria of consensus were developed into practice recommendations, supported by the results of the formal consensus and the evidence-based findings from systematic review.**

Results and Discussion: **A total of 23 studies were included in the systematic review; three randomized controlled trials (RCTs), 13 cohorts, two case–controls and three clinic-cases. Twenty-two practice recommendations for the management of chronic medication in the perioperative period resulted from formal consensus.**

What is new and Conclusion: **Epidemiological studies concerning the perioperative management of chronic medications are clinically heterogeneous and there are few RCTs available. However, the formal consensus method proved to be a helpful tool to integrate different strands of evidence for the development of practice guidelines.**

Keywords: **chronic medication, evidence-based practice, formal consensus, guidelines, perioperative period, systematic review**

WHAT IS KNOWN AND OBJECTIVE

The volume of surgery is huge worldwide and the number of interventions performed is increasing, due to advances in technological resources and refinement of medical teams' expertise, in a progressively elderly and sick population (1). Consequently, half of the general surgical patients take medications unrelated to surgery (2). Nevertheless, there is little evidence quantifying the risk of withdrawal or continuation of chronic medication in the perioperative period. Often, clinical decisions are empirical and inconsistent among clinicians. An observational study by Kennedy and

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colleagues found that taking a drug unrelated to surgery was associated with an increased relative risk of a post-operative complication by 2·7, compared with those who were not taking any drug. Of those patients, 5% suffered post-operative complications directly attributable to withdrawal of their chronic medication (2). These numbers strongly suggest that correct management of chronic medication in the perioperative period should become a substantial global public-health concern.

Evidence-based guidelines for perioperative medication management are therefore critically needed to improve patient safety in surgery. Although there are published guidelines, these are not consensual and do not present evidence level classification. The purpose of this work was to provide practice recommendations for the management of chronic medication in the perioperative period, using a formal consensus process to incorporate key evidence findings from both a systematic review and clinical expertise.

METHODS

Study selection

A systematic review was conducted in September 2008. First, we identified literature published in the last 10 years, in English, Spanish and French languages. We searched Medline, Embase, ISI Web of Knowledge and Medscape electronic databases, using combinations of the following terms: 'perioperative period', 'surgery', 'chronic medication', 'regular medication', 'drug related problems', 'adverse drug interactions', 'adverse drug events', 'adverse drug reactions', 'complications', 'drug therapy', 'drug withdrawal', 'polypharmacy', 'management of perioperative', 'anaesthesia'. These terms were conjugated with the Medical Subject Heading (MeSH) search for different therapeutic groups. Second, we screened titles and abstracts to exclude obviously non-eligible studies and then hand searched additional references from the references lists of relevant articles. All retrieved studies concerning chronic medication in the perioperative period were then included. Studies already pooled in meta-analysis, were excluded to avoid weighting duplicated data.

Additionally, we searched for published guidelines in electronic sites of evidence-based journals and several organizations, responsible for providing guidance on clinical practice (Table 1).

Quality assessment and data extraction

The quality of selected studies was evaluated by two independent investigators using the Scottish Intercollegiate Guidelines Network levels of evidence (SIGN) (3). Data were summarized in tables outlining the following information: study design, surgery type, patient characteristics, comparison groups, outcome measures and effect size.

For some therapeutic groups, we found evidence-based guidelines with strength classification. Those guidelines were adopted and no further analysis was performed. For the other therapeutic groups, with insufficient or conflicting evidence, a

Table 1. Electronic sites of evidence-based journals and specific organizations

Clinical evidence	http://www.clinicalevidence.bmj.com
Canadian Agency for Drugs and Technologies in Health	http://www.cadth.ca
Evidence-based medicine	http://www.ebm.bmj.com/
Institute for Clinical Systems Improve (ICSI)	http://www.icsi.org
National Heart Lung and Blood Institute (NHLBI)	http://www.nhlbi.nih.gov
National Institute for Health and Clinical Excellence (NICE)	http://www.nice.org.uk
National Guideline Clearinghouse™ (NGC)	http://www.guideline.gov
Scottish Intercollegiate Guideline Network (SIGN)	http://www.sign.ac.uk.com
Skyscape	http://www.skyscape.com
Therapeutic guidelines	http://www.tg.org.au/?sectionid=11
Therapeutics initiative	http://www.ti.ubc.ca
TRIP	http://www.tripdatabase.com/
Up-to-date	http://www.uptodate.com

formal consensus method was used to integrate the different sources of evidence.

Formal consensus

The formal consensus method used was based on a modified nominal group technique described by Rycroft-Malone (4). An interdisciplinary panel of eleven experts was invited by telephone and agreed to participate. This panel comprise specialists with recognized expertise in internal medicine, evidence-based medicine, surgery, anaesthesiology and pharmacy. Seven specialists completed all the rounds of the consensus process.

Thirty-two statements for the management of perioperative chronic medication were formulated, considering the literature retrieved by the systematic review and the other evidence-based resources outlined above. All statements were constructed in a similar manner to reduce bias. These statements were collated in a structured form and rated on a 1–9 Likert scale, where 1 represents the least agreement and 9 represents the most agreement level.

The panel was then surveyed by email and asked to rate their level of agreement with each individual statement, taking into account their clinical expertise and the realities of healthcare services in Portugal. Some of the studies classified above with the highest level of evidence were also sent for facultative support.

A face-to-face meeting was convened on March 2009. Each expert was given the results of the first-round survey, with the median rating of the group and the corresponding interquartile range (IQR) for each statement. The statements were discussed in turn, focusing primarily on those that were the source of most disagreement. All the members were given the opportunity to explain their point of view and invited to add suggestion.

During the meeting, two investigators registered the relevant conclusions that came out from the discussion. The panel also recommended some adjustments of the statements to clarify their meaning.

A second round survey was then conducted by e-mail and statements were re-rated. This second rating was then used to determine the final level of agreement with each statement. If the median score of a statement was 7–9 with an IQR range less than 3, this was considered to be agreement or 'consensus' and the statement was developed into a practice recommendation. Likewise, if it did not reach this level of consensus it was rejected.

The recommendations strength was classified according to SIGN grades (3).

RESULTS AND DISCUSSION

As illustrated in Fig. 1, the initial search yielded 3544 citations. After screening by one reviewer, 249 were identified as 'possibly eligible' for inclusion. Hand searching of references from the relevant articles identified 99 additional citations.

Of these, 325 were excluded after reviewing the full publication. The studies that evaluated β-blockers, statins and antithrombotic therapy during perioperative period were also excluded from systematic review since, for these therapeutic groups, clinical practice guidelines with strength classification were found. The American College of Cardiology/American Heart Association developed practice guidelines which define the management of chronic use β-blockers and statins in the perioperative period (5).

The American College of Chest Physicians (ACCP) published clinical practice guidelines for the perioperative management of antithrombotic therapy (6).

For some therapeutic groups, we found practice recommendations but these had no strength evidence classification and thus were not adopted, although they were used for comparative discussion.

Finally, a total of 23 studies were included in the systematic review. Data extracted from the studies and their evidence level are summarized in Table 2 for the different therapeutic groups.

Calcium channel blockers

No study comparing withdrawal and continuation of Calcium channel blockers (CCB) in the perioperative period was found. The literature search identified only three cohort studies assessing the effects of CCB on mortality during post-operative period, and one case–control study about the effect of CCB on post-operative silent myocar-

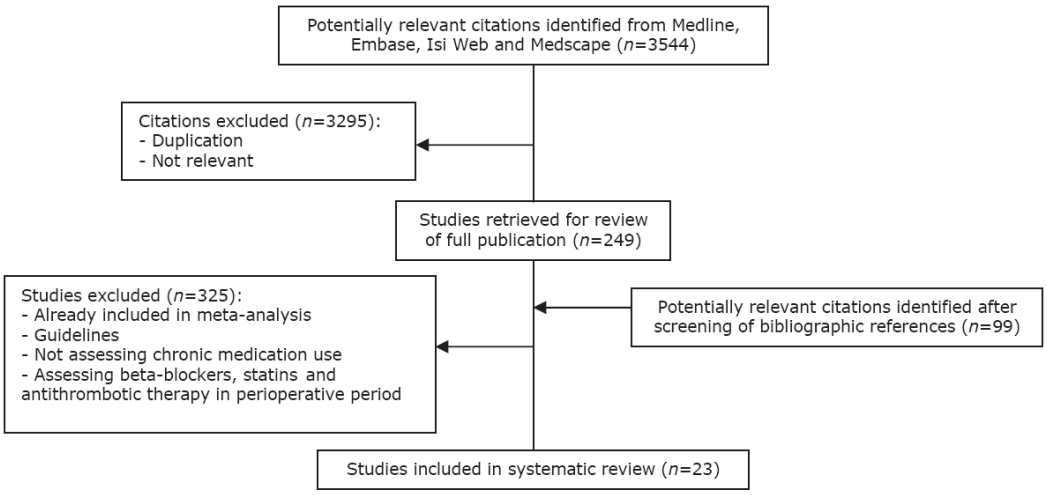

Fig. 1. Flow diagram of study selection process.

dial ischaemia (7–10). Of the three cohort studies, only Wijeysundera *et al.* (10), found that CCB were associated with significantly reduced in-hospital mortality, but where not associated with major bleeding. The other two cohort studies failed to show a beneficial effect of CCB on post-operative mortality (7, 9). The case–control study showed a higher incidence of post-operative silent myocardial ischaemia in patients receiving chronic CCB.

Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonist

Two randomized controlled trials (RCT) and one cohort study compared withdrawal with continuation of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor antagonist (ARA) during the perioperative period (11–13). One cohort study compared the administration of ARA in the morning of surgery with administration of ACEI 24 h before surgery (14). Another study (15) compared ACEI/ARA users with no users. These five studies found that intake of ACEI/ARA in the morning of surgery negatively affects haemodynamic control. Three of those studies (11, 12, 14) concluded that stopping ACEI/ARA on the day of surgery was associated with a minor number of hypotensive episodes in the post-induction period. Pigott *et al.* (13) verified that patients who stopped ACEI, had higher levels of arterial blood pressure, consequently needing less vasoconstrictors administration during surgery, but often requiring vasodilator infusions to prevent hypertension in the early post-operative period. Lee *et al.* (15) and Brabant *et al.* (14) concluded that patients who took ACEI or ARA medication on the surgery morning had significantly higher needs of vasopressors during surgery. Additionally, two case reports described refractory hypotension in patients treated with ACEI/ARB on the surgery morning. Two other studies (7, 9) evaluated the effect of ACEI on post-operative mortality; one found no effect but the other (7) observed a post-operative long-term mortality reduction in ACEI users.

Nitrates

No study comparing withdrawal with continuation of chronic nitrates in the perioperative period was found. Weightman *et al.* (9) suggest that there is an association, independent of other recognized risk factors, between pre-operative treatment with nitrates and increased in-hospital mortality after coronary artery surgery.

Diuretics

No study comparing withdrawal with continuation of chronic diuretics in the perioperative period was

Table 2. Characteristics of included studies

Study [Reference] Design	Surgery Type Patients	Comparison Groups	Outcome measures	Effect size	EL[i]
Calcium Channel Blockers (CCB)					
(7) Cohort	Cardiac surgery 6635 individuals	CCB users CCB non-users	In-hospital mortality	Odds ratio (95%CI[ii]) 0·56 (0·33–0·94) P^{iii} = 0·028	2^{++}
			Major Bleeding	1·01 (0·75–1·37) P = 0·94	
(8) Case-Control	General and Vascular surgery 453 patients All patients receiving chronic intercurrent medication continued this up to and including the morning of surgery, and recommenced as soon as feasible after the end of operation.	Cases: Patients with postoperative silent myocardial ischemia Controls: Patients with no postoperative silent myocardial ischemia	CCB use	Odds ratio (95% CI) 1·95 (1·15-3·32) P = 0·015	2^{+}
Angitensin converting enzyme inhibitors (ACEI) and Angiotensin Receptor Antagonist (ARA)					
(9) RCT	Cardiac surgery 40 Patients	1- Continue with their regular ACEI up until the day of surgery	Vasoactive drugs: Glyceryl trinitrate in theatre (mg) Glyceryl trinitrate in recovery (mg)	Comparison of means $P < 0·05$ $P < 0·05$	1^{-}
			Glyceryl trinitrate total (mg)	$P < 0·05$	
		2- Have the ACEI discontinued on the day before surgery	Metaraminol during surgery (mg)	$P < 0·05$	
			Numbers of patient requiring vasoactive drugs: Meraminol after induction Epinephrine after surgery Norepinephrine after surgery Epinephrine in recovery Norepinephrine in recovery Glyceryl trinitrate (<1 mg h^{-1}) after surgery Glyceryl trinitrate (<1 mg h^{-1}) in recovery Sodium nitroprusside in recovery	Comparison of number of patients Ns[iv] Ns Ns Ns Ns $P < 0·05$ $P < 0·05$ Ns	
			Systemic mean arterial pressure measured at intervals during the perioperative period	Comparison of means $P < 0·05$	
			Systemic vascular resistance measured at intervals during surgery and the early postoperative period	$P < 0·05$	

Table 2. (Continued)

Study [Reference] Design	Surgery Type Patients	Comparison Groups	Outcome measures	Effect size	EL[i]
(10) Cohort	General Surgery 267 Patients	1- Patients who took their last dose of ACEI or ARA < 10 hours before anaesthesia 2- Patients who took their last dose of ACEI or ARA ≥ 10 hours before anaesthesia	Blood pressure (at or shortly after induction), unplanned intensive care unit, hemodynamic instability in the postanaesthesia care unit (arterial blood pressure or heart rate), acute renal impairment, transient ischemic attack, stroke, myocardial ischemia/infarction, and death The only significant difference between de groups was moderate hypotension at 0–30 min after induction 1 vs 2	Any episode 1–60·4%; 2–46·3% $P = 0·02$ Odds Ratio(95% CI) P 1·74/ 1·03–2·93) $P = 0·04$	2^+
(11) RCT	Vascular Surgery 37 Patients	Group I - ARA discontinued on the day before surgery Group II - ARA given 1h before aesthesia	Systolic arterial pressure Episodes of hypotension Number of patients with hypotension episodes Duration of hypotension episodes Need for vasoactive drugs	Group II < Group I at 5, 15, and 23 min after induction $P < 0·05$ Group I – 1 Group II – 2 $P < 0·01$ Group I – 12 Group II – 19 $P < 0·01$ Group I – 3 ± 4 min Group II – 8 ± 7 min $P < 0·01$ Group II > Group I – $P < 0·02$	1^-
(12) Cohort	Vascular surgery 84 patients	ARA users ACEI users ARA was given until the morning of surgery, whereas the last administration of ACEI was 24 hours before surgery	Patients with hypotension ARA users compared with ACEI users Patients with refractory hypotension ARA users compared with ACEI users Ephedrine requirements until 30 minutes after the induction of anaesthesia ARA users compared with ACEI users	Comparison of proportions P ≤ 0·05 P ≤ 0·05 Comparison of means P ≤ 0·001	2^+
(13) Cohort	Vascular surgery 80 patients	ACEI users (take in the surgery morning) ACEI non-users	Systemic haemodynamic variables at 5 points during surgery (Heart rate; Mean arterial pressure; Cardiac Output; Mixed venous oxygen saturation; Systemic vascular resistance) Total amount of noradrenaline infused Number of patients requiring noradrenaline	Only the cardiac output was significantly greater in ACEI non-users_$P < 0·05$ ACEI users > ACEI non-users $P < 0·05$ Ns	2^+

Table 2. (Continued)

Study [Reference] Design	Surgery Type Patients	Comparison Groups	Outcome measures	Effect size	EL[i]
(14) Clinic Case	A 75 years old man submitted first an endaterectomy of the right and 2 months later of the left internal carotid artery. He takes nicardipine and enalapril to treat hypertension. **1st Surgery** – Enalapril was withdrawn the eve of surgery, but nicardipine was given before surgery. Blood pressure (BP) decreased 4 minutes after induction by more 30% below the preoperative value. Despite repeated IV ephedrine administration (up to 27 mg), BP decreased to 88/46 mmHg and heart rate 46 bpm. A bolus of 1 mg of terlipressin was administered IV 9 minutes after induction, BP increase to 118/53 mmHg 1 minute later and remained stable during the anaesthesia period. **2nd Surgery** – 10 days prior to surgery, enalapril was withdrawn and replaced by ibersartan. Preoperative blood pressure was 150/70 mmHg. Three hours before surgery, irbesartan and nicardipine were given. Blood pressure decreased 3 minute after induction to 92/44 mmHg. Despite repeated IV ephedrine administrations (up to 18 mg), BP decreased on 5th minute to 47/30 mmHg. BP increased after IV phenylephedrine administrations to 88/66 mHg but decreased again to 79/46 mmHg despite the administration of IV ephedrine. 20 minutes after induction of anaesthesia, terlipressin 1 mg bolus was administered. BP increased after 1 minute to 102/50 mmHg but decreased again to 78/52 mmHg. Administrations of terlipressin, 1 mg were repeated on the 17th and on 35th minute after induction until BP increased to 118/72 mmHg and remained stable during the entire anaesthesia period. No neurological or cardiac postoperative complications occurred.				3
(15) Clinic Case	A 71 years old woman submitted to thyroid lobectomy. She was being chronically treated with ACEI, which were taken until the morning of surgery. After induction of anaesthesia, arterial hypotension refractory to crystalloid therapy developed and worsened in spite of administration of a gelatin-type colloid (Gelafundina®). The patient did not respond to ephedrine or dopamine and required stabilization with adrenalin in continuous perfusion for 12 hours. Later evolution was satisfactory and recovery took place without sequelae.				3
CCB, ACEI and Nitrates					
(16) Prospective Cohort	Major vascular surgery 1693 patients, mean age 65 years	ACEI users ACEI non users CCB users CCB non-users	In-hospital mortality in patients who use: ACEI CCB Long-term mortality **ACEI** CCB	Logistic regression models Odds ratio (95%CI) 0·69 (0·44–1·09) $P = 0·09$ 0·92 (0·60–1·40) $P = 0·76$ Hazard Ratio (95%CI) **0·74 (0·59–0·92)** ***P* = 0·008** 0·80 (0·61–1·05) $P = 0·12$	2+
(17) Cohort	Cardiac surgery 1593 Patients, mean age 63·8 years. Cardioactive drugs was continued until the morning of surgery	Nitrates users CCB users ACEI users Digoxin users Nitrates non-users CCB non-users ACEI non-users Digoxin non-users	In-hospital deaths in patients who use: **Nitrates** CCB ACEI Digoxin	Relative risk (95% CI) **3·8 (1·5–9·6)** 1·1 (0·6–2·1) 0·8 (0·4–1·5) 0·7 (0·2–1·8)	2+

Table 2. (Continued)

Study [Reference] Design	Surgery Type Patients	Comparison Groups	Outcome measures	Effect size	EL[i]
Diuretics					
(18) Cohort	Noncardiac surgery 12381 operative cases	Group I - ACEI or ARA users Ia) Diuretics users Ib) CCB users Ic) Diuretics and CCB users Id) Diuretics and CCB non-users Group II - ACEI and ARA non-users IIa) Diuretics users IIb) CCB users IIc) Diuretics and CCB users IId) Diuretics and CCB non-users ACEI/ARA users withhold the medication the day of surgery	Mean number of episodes of hypotension < 70 mmHG	**Ia vs IIa P = 0·003** Ib vs IIb Ns Ic vs IIc Ns Id vs IId Ns	2[+]
			Mean number of episodes with a 40% decrease in systolic blood pressure	**Ia vs IIa P = 0·02** Ib vs IIb Ns Ic vs IIc Ns Id vs IId Ns	
			Mean number of episodes with a 50% decrease in systolic blood pressure	**Ia vs IIa P = 0·02** Ib vs IIb Ns Ic vs IIc Ns Id vs IId Ns	
			Mean number of vasopressor boluses administered	**Ia vs IIa P = 0·02** Ib vs IIb Ns Ic vs IIc Ns Id vs IId Ns	
			Postoperative myocardial infarction	Ia vs IIa Ns Ib vs IIb Ns Ic vs IIc Ns Id vs IId Ns	
			Renal failure	Ia vs IIa Ns Ib vs IIb Ns Ic vs IIc Ns Id vs IId Ns	
Hormone Replacement Therapy					
(19) Cohort	Vascular surgery 734 Women older than 54 years	Estrogen users Estrogen non-users	*Mortality*	Odds ratio (95% CI) 0·38 (0·07–1·21)	2[−]
			Perioperative cardiac morbidity (myocardial infarction, unstable angina, atrial fibrillation, ventricular fibrillation, ventricular tachycardiac, cardiogenic shock or complete heart block)	0·52 (0·23–1·7)	
			Late complications (perioperative cardiac morbidity, infections morbidity, permanent cerebral vascular accident, gastrointestinal complications, multisystem failure, pulmonary embolus, ventilator support for more than 5 days, renal failure requiring dialysis, deep vein thrombosis and acute limb ischemia)	0·42 (0·16–0·96)	
			Early complications (repeat surgery for tamponade, aortic dissection or bleeding)	0·98 - Estrogens users 1·11 - Estrogen non-users	
			Length of stay	7·0 ± 0·36 – Estrogen users 8·5 ± 0·95 – Estrogen non-users	

Table 2. (Continued)

Study [Reference] Design	Surgery Type Patients	Comparison Groups	Outcome measures	Effect size	EL[i]
(20) Cohort	Vascular surgery 4782 patients	1-HRT users 2-HRT non-users 3-Men	*Postoperative outcomes* (myocardial infarction, congestive heart failure, central nervous system complication, renal dysfunction, red blood cell transfusion, fresh frozen plasma transfusion, platelet transfusion, duration o hospital stay) *Mortality* 1 vs 2 2 vs 3 1 vs 3	There were no significant differences in the incidence of postoperative outcomes in the 3 groups. Odds ratio (95% CI) P 0·7 (0·2–2·1) 0·51 0·8 (0·5–1·2) 0·30 0·9 (0·3–2·5) 0·79	2^{++}
(21) Case-control	Orthopedic surgery 318 patients	HRT or selective oestrogen receptor modulators users HRT or selective oestrogen receptor non-users	Postoperative thrombosis	Odds ratio (95% 0·68 (0·35-1·28)	2^{+}
Tricyclic antidepressants					
(22) RCT	Orthopedic surgery 120 patients	1 - Tricyclic users who continued antidepressants before surgery 2 - Tricyclic users who discontinued antidepressants 72 h before surgery and then are resumed on the day after surgery 3 - Antidepressants non-users	Hypotension during anaesthesia Arrhythmias during anaesthesia Delirium or confusion The day before operation The day of the operation Postoperative day 1 2 3	Comparison of groups 1 - 2 – 3 8% 5% 0% 5% 5% 3% 0% 0% 0% P = Ns 0% 15% 0% P = 0·01 3% 10% 0% P = Ns 10% 5% 3% P = Ns 0% 0% 0% P = Ns	1^{-}
(23) Cohort	Orthopedic surgery 70 patients	Tricyclic users (discontinued on the day of the operation and restarted the next day) Antidepressants non-users	Postoperative Shivering Tryciclic users No depressed patients	Comparison of groups 8/35 2/35 P = 0·04	2^{+}
(24) Clinic case	57-years-old man submitted to cardiac surgery, that take chronic clomipramine had severe, refractory hypotension during anaesthesia. The authors hypothesize that preoperative postural hypotension may be a risk factor for tricyclic related hypotension during anaesthesia.				3
(25) Clinic case	61-years-old woman submitted to gynaecology surgery, that take chronic amitriptyline had severe, refractory hypotension during anaesthesia.				

Table 2. (Continued)

Study [Reference] Design	Surgery Type Patients	Comparison Groups	Outcome measures	Effect size	EL[i]
Serotonin reuptake inhibitors (SSRIs)					3
(26) Cohort	Orthopedic surgery 520 individuals	1- Serotonergic antidepressants users 2- Non serotonergic antidepressants users 3- Antidepressants non-users	Need for blood transfusion 1 vs 3 2 vs 3	Odds ratio (95%CI) 3·71 (1·35–10·18) 0·74 (0·1–5·95)	2⁺
(27) Cohort	Vascular surgery 4794 patients	SSRIs users SSRIs non-users	 All cause mortality Rehospitalization Composite end point (all cause mortality or rehospitalization)	Hazard ratio (95% CI) *P*-value 1·61 (1·17–2·21) *P* = 0·003 1·52 (1·30–1·77) *P* < 0·0001 1·46 (1·26–1·70) *P* < 0·0001 Kaplan-Meier mortality estimate Nearly 10% absolute excess mortality in the SSRIs users	2⁺
(28)	49-year-old women, submitted to cardiac surgery, which pre-operative medication included clonazepam 0·5 mg daily, seroquel 25 mg twice daily and paroxetine 40 mg daily for anxiety and depression in postoperative period, she woke confused and agitated. Her temperature was 40°C. Neurologic examination revealed myoclonic jerks, fine tremors of the extremities, dilated pupils, shivering, hyperactive reflexes and hypertonicity. A diagnosis of serotonin syndrome was made.				3
Glucocorticoids					
(29) Cohort	Hand and wrist surgery 80 patients with rheumatoid arthritis, mean age 53 years All patients received their regular medication throughout the perioperative period	A-Methotrexate only B-Steroids only C-Steroids and Methotrexate D-Neither drug	Wound infections A e C /B e D B e C/A e D Wound infection and dehiscence rates A/B/C/D Wound infection -diabetic rheumatoid patient -non diabetic rheumatoid patient	Comparison of proportions *P* = 1·0 *P* = 0·21 Ns Rate (CI 95%) 33% (9·7–70) 3·3% (1·3–8·1)	2⁻

found. One study evaluated the association between ACEI/ARA therapy and the haemodynamic control of patients undergoing non-cardiac surgery and concluded that chronic diuretic therapy is associated with more frequent hypotension episodes in ACEI/ARA-treated patients (16).

Hormone replacement therapy

No study comparing withdrawal with continuation of hormone replacement therapy (HRT) in the perioperative period was found. Two cohort studies evaluated morbidity and mortality in HRT users and HRT non-users (17, 18). The two studies concluded that HRT administration had no effect on mortality or morbidity rates in women undergoing vascular surgery. One case–control study found no association between perioperative HRT and post-operative thrombosis in patients undergoing major orthopaedic surgery (19).

Tricyclic antidepressants

One randomized controlled trial (20) compared withdrawal of tricyclic antidepressants with continuation in the perioperative period and concluded that the incidence of intraoperative hypotension and arrhythmias was lower in patients taking antidepressants, whether treatment was stopped pre-operatively or not. On the other hand, discontinuation of antidepressants was associated with increased incidence of delirium, confusion and depressive symptoms. One cohort study showed a significantly higher incidence of post-shivering in depressed patients (21). Two clinic cases described severe, refractory hypotension during anaesthesia associated with chronic tricyclic antidepressant therapy (22, 23).

Serotonin reuptake inhibitors

No study comparing withdrawal of serotonin reuptake inhibitors (SSRIs) with continuation in the perioperative period was found. Two cohort studies (24, 25) compared different endpoints between SSRIs users and non-users. Movig *et al.* (24) concluded that the use of SSRIs is associated with increased risk of bleeding and subsequent need of blood transfusions during orthopaedic surgery. The other study verified that SSRI use before surgery was associated with a higher risk of long-term post-operative mortality and re-hospitalization (25). We also found one clinical case of serotonin syndrome following cardiac surgery, in a woman who had paroxetine in the pre-operative period (26).

Glucocorticoids

Only one study assessing the chronic use of steroids in the perioperative period was found. This cohort study found no statistically significant risk of wound infection or breakdown in patients taking steroids, methotrexate or both (27).

Formal consensus. From the second round rating, nine of the 32 statements did not meet the established criteria of consensus/agreement (median score from 7 to 9 and IQR less than 3) (Table 3). The remaining statements were developed into practice recommendations, supported by the results of the formal consensus process and the evidence-based findings from the systematic review.

Our results clearly show that there is a lack of experimental randomized evidence on perioperative risk management of chronic medication. Sometimes, this evidence is controversial and not completed with observational studies. Consequently, the 23 practice recommendations developed for the management of chronic medication in the perioperative period are supported mainly by observational cohort studies and formal consensus. For some therapeutic groups, for which no studies were found, physiologic and pharmacologic plausibility was considered to justify the recommendation.

Calcium channel blockers

Patients currently taking CCB and scheduled for surgery, should continue CCB until the day of surgery, inclusively. After surgery, CCB should be restarted with oral intake. *Strength of recommendation*: C

Rationale: This recommendation is supported by the formal consensus (median score 9, IQR 0) and by extrapolated evidence from a cohort study (10), with evidence level of 2^{++}. This study did not compare withdrawal with suspension of CCB in perioperative period, but found no association between CCB chronic use and major bleeding in patients submitted to vascular surgery. It also concluded that CCB use was associated with significantly reduced in-hospital mortality.

Seven recommendations (28–34) were published in accordance with our recommendation.

Table 3. Statements of formal consensus

Calcium channel blockers (CCB)

For patients currently taking CCB and scheduled for surgery, CCB should be continued until the day of surgery, inclusively. After surgery, CCB should be restarted with oral intake.

							1		6	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 9 Interquartile range – 0

If the patient cannot take oral medications, it may be necessary intravenous (IV) substitution, if poor haemodynamic condition occurs (hypertension or arrhythmia).

							2	3	2	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 8 Interquartile range – 1

Angiotensin-converting enzyme inhibitors (ACEI)

For patients currently taking ACEI scheduled for surgery, ACEI should be withdrawn on the morning of surgery. After surgery, ACEI should be restarted with oral intake.

								2	5	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 9 Interquartile range – 0·5

*For patients currently taking ACEI for the management of hypertension and scheduled for surgery, ACEI should be continued until the day of surgery inclusively. After surgery, ACEI should be restarted with oral intake.

	2	1					1	2	1	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 7 Interquartile range – 6·5

If the patient cannot take oral medications, it may be necessary IV substitution, namely if poor haemodynamic condition occurs (hypertension or heart failure). However, as there is no IV form available, consider parental β-blockers or CCB.

							2	1	3	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 8 Interquartile range – 2

Angiotensin receptor antagonist (ARA)

For patients currently taking ARA and scheduled for surgery, ARA should be withdrawn on the morning of surgery. After surgery, ARA should be restarted with oral intake.

							1		6	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 9 Interquartile range – 0

Nitrates

For patients currently taking nitrates and scheduled for surgery, nitrates should be continued until the day of surgery, inclusively. After surgery, nitrates should be restarted with oral intake.

									7	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 9 Interquartile range – 0

Diuretics

For patients currently taking diuretics and scheduled for surgery, diuretics should be withdrawn on the day of surgery and restarted with oral fluid intake.

							2	2	3	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 8 Interquartile range – 1·5

α_2-Agonists

For patients currently taking α_2-agonists and scheduled for surgery, α_2-agonists should be continued until the day of surgery, inclusively. After surgery, α_2-agonists should be restarted with oral intake.

							2	1	4	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Table 3. (Continued)

Median – 9 Interquartile range – 1·5										
Digoxin										
For patients currently taking digoxin and scheduled for surgery, digoxin should be continued until the day of surgery, inclusively. After surgery, digoxin should be restarted with oral intake.										
					1	1	1		4	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 9 Interquartile range – 2·5										
*If the patient has instable arrhythmia or heart failure, consider possible IV administration.										
	1			1			1	2	3	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 8 Interquartile range – 3·5										
Niacin, fibrates, cholestyramine and colestipol										
For patients currently taking niacin, fibric acid derivatives or bile sequestrants and scheduled for surgery, this medications should be discontinued 1 day before surgery and restarted with oral fluids intake.										
						1		1	5	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 9 Interquartile range – 0·5										
Oral contraceptives (OC)										
*For patients currently taking OC and scheduled for surgery, OC should be stopped 4 or 6 weeks before surgery.										
	2	2						1	2	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 3 Interquartile range – 5										
If the patient is submitted to procedures with low to moderate risk of thromboembolism, OC should be continued until the day of surgery, inclusively.										
If the patient is submitted to procedures with high risk of thromboembolism, OC should be continued until the day of surgery, inclusively, and the patient should have thromboprophylaxis in the perioperative period.										
		1			1		1	2	2	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 8 Interquartile range – 2·5										
*After surgery, OC should be restarted with oral intake.										
	3	1	1				1		1	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 2 Interquartile range – 4										
OC should be restarted after surgery, at the time the patient has the first menstruation and recovers mobility.										
							1		6	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 9 Interquartile range – 0										
Hormone replacement therapy (HRT)										
*For patients currently taking HRT and scheduled for surgery, HRT should be stopped 4 or 6 weeks before surgery.										
	1				1		1	1	3	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 8 Interquartile range – 3										
*If the patient is submitted to procedures with low to moderate risk of thromboembolism, HRT should be continued until the day of surgery, inclusively.										
If the patient is submitted to procedures with high-risk thromboembolism, HRT should be continued until the day of surgery, inclusively, and the patient should have thromboprophylaxis in the perioperative period.										
	2					1	1	1	1	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Table 3. (Continued)

Median – 6 Interquartile range – 6
*After surgery, HRT should be restarted with oral intake.

	4		1		1			1		
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 1 Interquartile range – 3
†HRT should be restarted after surgery when the patient recovers mobility.

							1		6	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 9 Interquartile range – 1

Tricyclic antidepressants (TCAs)

For patients currently taking TCAs and scheduled for surgery, TCAs should be continued until the day of surgery, inclusively. After surgery, TCAs should be restarted with oral intake.

			1					1	5	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 9 Interquartile range – 0·5

Serotonin reuptake inhibitors (SSRIs)

For patients currently taking SSRIs and scheduled for surgery, SSRIs should be continued until the day of surgery, inclusively. After surgery, SSRIs should be restarted with oral intake.

		1						3	3	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 8 Interquartile range – 1

If the patient is submitted to procedures with a high risk of operative bleeding, SSRIs should be withdrawn according to their half-life. After surgery, SSRIs should be restarted with oral intake.

						1	1	3	2	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 8 Interquartile range – 1

Monoamine oxidase inhibitors (IMAO)

For patients currently taking IMAO and scheduled for surgery, if IMAO-safe technique anaesthesia is used, IMAO should be continued until the day of surgery, inclusively. If IMAO-safe technique anaesthesia cannot be used, IMAO should be discontinued 2 weeks before surgery. After surgery, IMAO should be restarted with oral intake.

	1					1	2	1	2	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 7 Interquartile range – 2

Insulin

For patients currently taking subcutaneous insulin and scheduled for surgery, the usual dose should be administered in the day before surgery. In the perioperative period, glucose levels should then be assessed and adequate doses of rapid acting insulin should be administered. The normal insulin schedule should be restarted with oral food intake.

						1	1	2	3	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 8 Interquartile range – 1·5

Oral hypoglycemics (OH)

For patients currently taking OH and scheduled for surgery, OH should be stopped, according to their half-life. After surgery, OH should be restarted with oral intake. If diabetes is poorly controlled insulin should be administered in the perioperative period.

								1	6	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Median – 9 Interquartile range – 0

Non-steroidal anti-inflammatory drugs (NSAIDs)

*For patients currently taking NSAIDs and scheduled for surgery, NSAIDs should be withdrawn before surgery, according to their half-life. After surgery NSAIDs should be restarted with oral intake.

	1	1					1	1	3	
Disagree	1	2	3	4	5	6	7	8	9	Agree

Table 3. (Continued)

Median – 8 Interquartile range – 4·5										
*For patients currently taking NSAIDs and scheduled for surgery, NSAIDs can be continued during the perioperative period.										
	1	1					3		2	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 7 Interquartile range – 3·5										
Thyroid hormones										
Patients taking thyroid hormones, should take the usual dose until the morning of surgery. After surgery, medication should be restarted with oral intake.										
						1			6	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 9 Interquartile range – 0										
Antithyroid agents										
Patients taking antithyroid agents should take the usual dose until the morning of surgery. After surgery, medication should be restarted with oral intake.										
							1		6	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 9 Interquartile range – 0										
Glucocorticoids										
For patients currently taking glucocorticoids and scheduled for surgery, glucocorticoids should be continued until the day of surgery, inclusively. After surgery, glucocorticoids should be restarted with oral intake.										
	1							1	5	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 9 Interquartile range – 1·5										
If the patient is taking more than 5 mg/day of prednisolone (or equivalent), or might have some degree of hypothalamic–pituitary–adrenocortical axis suppression, supplemental hydrocortisone doses should be given.										
							2	2	3	
Disagree	1	2	3	4	5	6	7	8	9	Agree
Median – 8 Interquartile range – 1·5										

*Statements did not meet the established criteria of consensus.
†Did not make sense.

If the patient cannot take oral medications and poor haemodynamic condition occurs (hypertension or arrhythmia), intravenous (IV) substitution of CCB may be necessary. *Strength of recommendation*: D

Rationale: This recommendation is only supported by the formal consensus (median score 8, IQR 1). The consensus panel agreed that an episode of hypertension might require IV administration of CCB if the patient cannot take oral medication.

Angiotensin converting enzyme inhibitors and angiotensin receptor antagonist

In patients currently taking ACEI or ARA scheduled for surgery, the medication should be withdrawn on the morning of surgery. After surgery, ACEI should be restarted with oral intake.

Strength of recommendation: C

Rationale: This recommendation is supported by the formal consensus (median 9, IQR 0·5), by evidence from two cohort studies (strength of evidence 2^+) (12, 14) and by evidence from two clinic cases (strength of evidence 3) (35, 36).

Several studies show that continuing chronic ACEI or ARA up to the time of surgery results in increased incidence of hypotension episodes and increased need of vasoconstrictors in the perioperative period, but possibly a reduced incidence of post-operative hypertension (11–15). Two clinic cases also described refractory hypotension associated with ACEI or ARA use (35, 36).

These results and two published guidelines (30, 34) are in accordance with our recommendation. The formal consensus panel agreed that the better approach is to withdrawal ACEI and

ARA before surgery, because a hypertension episode it is easier to reverse than a hypotensive episode.

Nevertheless, some authors (31, 32) recommend continuing ACEI in hypertensive patients during the perioperative period, because in the study of Comfere *et al.* (12) patients who omitted their ACEI required vasodilators administration more often to control hypertension in the early post-operative period.

If the patient cannot take oral medications and poor haemodynamic condition occurs (hypertension or heart failure), IV substitution of ACEI or ARA may be necessary. However, as there is no IV form available, consider parental β-blockers or CCB administration.

Strength of recommendation: D

Rationale: This recommendation is supported by the formal consensus (median 8, IQR 2). Again, the formal consensus experts agreed that an episode of hypertension might require IV administration if the patient cannot take oral medication.

Nitrates

Patients currently taking nitrates and scheduled for surgery, should continue nitrates until the day of surgery, inclusively. After surgery, nitrates should be restarted with oral intake.

Strength of recommendation: D

Rationale: This recommendation is supported by the formal consensus (median 9, IQR 0). Moreover, one cohort study found an association between preoperative treatment with nitrates and increased in-hospital mortality after coronary artery surgery (9). However, the authors do not recommend withdrawal of nitrates before coronary artery surgery because of possible rebound coronary vasoconstriction and worsening of myocardial ischaemia. Three recommendations were published in accordance with our recommendation (30, 34, 37).

Diuretics

Patients currently taking diuretics and scheduled for surgery, should withdraw diuretics on the day of surgery and restart with oral fluid intake.

Strength of recommendation: D

Rationale: This recommendation is supported by the formal consensus (median score 8, IQR 1·5) and by extrapolated evidence from a cohort study (16), with evidence level of 2^+. This cohort study (16) concluded that chronic diuretic therapy is associated with more frequent hypotension in ACEI/ARA-treated patients, compared with ACEI/ARA non-users, in spite of holding diuretic and ACEI/ARA therapy in the morning of surgery.

The systemic vasodilatation induced by the anaesthetic drugs may cause hypotension in patients taking diuretics. In the consensus meeting, the expert panel agreed that it is easier to reverse a possible episode of hypertension than hypovolaemia and hypokalaemia. However, in cases of heart failure, the patient may need IV diuretics. Four recommendations were published in accordance with our recommendation (29, 32–34).

α_2-Agonists

Patients currently taking α_2-agonists and scheduled for surgery, should continue α_2-agonists until the day of surgery, inclusively. After surgery, α_2-agonists should be restarted with oral intake.

Strength of recommendation: D

Rationale: This recommendation is supported by the formal consensus (media 9, IQR 1·5). The formal consensus panel agreed that α_2-agonists should be continued in the perioperative period, because they are usually prescribed in hypertensive cases of difficult control. On the other hand, abrupt withdrawal of these agents can precipitate rebound hypertension. Potential benefits of continuing α_2-agonists perioperatively include decrease in the stress response to surgery procedures and the reduction of anaesthetic doses because of their sedative, anxiolytic, analgesic and anti-shivering properties (32). Three recommendations were published in accordance with our recommendation (29, 32, 34).

Digoxin

Patients currently taking digoxin and scheduled for surgery, should continue digoxin until the day of surgery, inclusively. After surgery, digoxin should be restarted with oral intake.

Strength of recommendations: D

Rationale: This recommendation is supported by the formal consensus (media 9, IQR 2·5).

Pre-operative discontinuation of digoxin is not recommended given the risk of complication of the underlying disease and because the drug would need to be stopped some days before surgery owing its long half-life. Five recommendations were published in accordance with our recommendation (28, 30, 33, 34, 37). The Drug and Therapeutics Bulletin highlighted that in cases of arrhythmia IV administration of antiarrhythmics might be necessary (38). During the meeting, some experts agreed with our statement, that IV administration might be necessary if the patient has instable arrhythmia or heart failure. However, this practice did not meet the established criteria of consensus.

Niacin, fibrates, cholestyramine and colestipol

Patients currently taking niacin, fibric acid derivatives or bile sequestrants and scheduled for surgery, should discontinue these medications one day before surgery and restart them with oral fluids intake.

Strength of recommendation: D

Rationale: This recommendation is supported by the formal consensus (median 9, IQR 0·5). Niacin and fibrates are known to cause myopathy and rhabdomyolysis, a risk increased by surgery (32). On the other hand, the formal consensus panel agreed that these are not essential therapy. Three recommendations were published in accordance with our recommendation (32–34).

Oral contraceptives

If the patient is submitted to procedures with low to moderate risk of thromboembolism, oral contraceptives (OC) should be continued until the day of surgery, inclusively.

If the patient is submitted to procedures with high risk of thromboembolism, OC should be continued until the day of surgery, inclusively, and the patient should have thromboprophylaxis in the perioperative period.

OC should be restarted after surgery, when the patient has the first menstruation and recovers mobility.

Strength of recommendation: D

Rationale: These recommendations are supported by formal consensus, median 8, IQR 2·5 and median 9, IQR 0, respectively. The decision to continue or to stop OC before surgery must balance the risk of unwanted pregnancy against the risk of thromboembolism.

Some recommendations (37, 39) and the formal consensus panel agree that, ideally, OC should be stopped at least 4 weeks before the surgery (32), but the benefits and the risks of perioperative thromboembolism vs. perioperative pregnancy should be discussed with each patient.

Some experts defend that the risk of giving anaesthesia to a pregnant woman is higher than the risk of thromboembolism. Therefore, OC should be continued and the need for thromboprophylaxis therapy considered.

Tricyclic antidepressants

Patients currently taking tricyclic antidepressants (TCAs) and scheduled for surgery, should continue TCAs until the day of surgery, inclusively. After surgery, TCAs should be restarted with oral intake.

Strength of recommendation: D

Rationale: This recommendation is supported by the formal consensus (median 9, IQR 0·5). Also we found one randomized controlled trial (20), although with evidence level 1^{-}, where the patients on chronic TCA had a lower incidence of intraoperative hypotension and arrhythmias, independently of whether treatment was ceased pre-operatively or not. On the other hand, discontinuation TCAs was associated with increased incidence of delirium, confusion and depressive symptoms. Four published recommendations were in agreement with our recommendation (29, 32, 33, 40).

Serotonin reuptake inhibitors

Patients currently taking SSRIs and scheduled for surgery, should continue SSRIs until the day of surgery, inclusively. After surgery, SSRIs should be restarted with oral intake.

Strength of recommendation: D

Rationale: This recommendation is supported by the formal consensus (median 8, IQR 1). As the wash-out period of SSRIs may be as long as 3 weeks and clinical benefit from readministration may take several weeks, stopping SSRIs could lead to exacerbation of mood disorders. Four published

recommendations are in agreement with our recommendation (32, 33, 37, 41).

If the patient is submitted to procedures with high risk of operative bleeding, SSRIs should be withdrawn according to their half-life. After surgery, SSRIs should be restarted with oral intake.

Strength of recommendation: D

Rationale: This recommendation is supported by the formal consensus (median 8, IQR 1) and by a cohort study (24) (evidence level of 2^{+}). This cohort study concluded that the use of SSRIs is associated with an increased risk of bleeding and subsequent need for blood transfusion during orthopaedic surgery (24). One published recommendation agrees with our recommendation (32).

Monoamine oxidase inhibitors

For patients currently taking monoamine oxidase inhibitors (MAOI) and scheduled for surgery, if MAOI-safe technique anaesthesia is used, MAOI should be continued until the day of surgery, inclusively. If MAOI-safe technique anaesthesia cannot be used, MAOI should be discontinued 2 weeks before surgery. After surgery, MAOI should be restarted with oral intake.

Strength of recommendation: D

Rationale: This recommendation is supported by the formal consensus (median 7, IQR 2). MAOI use leads to accumulation of biogenic amines in the central and autonomic nervous systems. During anaesthesia, concomitant administration of sympathomimetic agents, like ephedrine, can result in massive release of stored norepinephrine and subsequent severe hypertension. In addition, administration of dextromethorphan and meperidine (pethidine) with MAOI can cause serious serotonin syndrome (32). Our recommendation is in accordance with these facts. Three other published recommendations also agree with our recommendation (32, 37, 40).

Insulin

Patients currently taking subcutaneous insulin and scheduled for surgery, should administer the usual dose in the day before surgery. In the perioperative period, glucose levels should then be assessed and adequate doses of rapid acting insulin should be administered. The normal insulin schedule should be restarted with oral food intake.

Strength of recommendation: D

Rationale; This recommendation is supported by the formal consensus (median 8, IQR 1·5). We found several insulin protocols (31, 33, 40, 42–44) in the literature for the perioperative management of insulin diabetic patients; however, there is no comparison study between protocols. Therefore, this topic was discussed in the formal consensus meeting.

Oral hypoglycaemics

Patients currently taking oral hypoglycaemics (OH) and scheduled for surgery, should stop OH, according to their half-life. After surgery, OH should be restarted with oral intake. If diabetes is poorly controlled, insulin should be administered in the perioperative period.

Strength of recommendation: D

Rationale: This recommendation is supported by the formal consensus (median 9, IQR 0). Sulphonylureas should be suspended 24–48 h before surgery, according to their half-life and renal function of the patient, to avoid hypoglycaemia. Metformin should be discontinued 48 h before anaesthesia to avoid lactic acidosis in situations of impaired tissue oxygenation (43). Inhibitors of α-glycosidases act on intestinal absorption of carbohydrates and therefore are not necessary during restricted food intake of the perioperative period (43). Ten published recommendations agree with our recommendation (28, 29, 31, 33, 37, 40, 42–45).

Thyroid hormones

Patients taking thyroid hormones should take the usual dose until the morning of surgery. After surgery, medication should be restarted with oral intake.

Strength of recommendation: D

Rationale: This recommendation is supported by the formal consensus (median 9, IQR 0). Thyroid hormones regulate important functions such as cardiac contractility, vascular tone, water and electrolyte balance and normal function of the central nervous system. It is now widely accepted than an euthyroid state marked by

adequate levels of thyroid hormones is necessary to obtain the best possible results from any kind of surgical intervention (46). Three published recommendations agree with our recommendation (31, 33, 40).

Antithyroid agents

Patients taking antithyroid agents should take the usual dose until the morning of surgery. After surgery, medication should be restarted with oral intake.

Strength of recommendation: D

Rationale: This recommendation is supported by the formal consensus (median 9, IQR 0). As with hypothyroidism, hyperthyroidism affects many body systems and influence surgical outcomes. In addition, patients with hyperthyroidism are at increased risk of thyroid storm, a potentially life-threatening condition that presents with fever, tachycardia, and confusion and may quickly lead to cardiovascular collapse and death. It can occur in the inadequately treated or undiagnosed hyperthyroid patient during, or soon after, surgery (42, 47). Two published recommendations agree with our recommendation (28, 33).

Glucocorticoids

Patients currently taking glucocorticoids and scheduled for surgery, should continue glucocorticoids until the day of surgery, inclusively. After surgery, glucocorticoids should be restarted with oral intake.

Strength of recommendation: D

If the patient is taking more than 5 mg/day of prednisone (or equivalent), or might have some degree of hypothalamic–pituitary–adrenocortical axis (HPA) suppression, supplemental hydrocortisone doses should be given.

Strength of recommendation: D

Rationale: These recommendations are supported by the formal consensus, median 9, IQR 1·5 and median 8, IQR 1·5, respectively. Physiologic stress inherent to surgery procedure activates HPA axis and increases corticotrophin (ACTH) and cortisol secretion. Exogenous glucocorticoids can suppress the HPA axis and the patient on chronic glucocorticoids may not produce sufficient levels of ACTH and cortisol to meet physiologic needs. Therefore, adrenal insufficiency with hypotension and shock may occur (42). To prevent this life-threatening complication, supplemental glucocorticoids ('stress dose' steroids) should be given perioperatively to those patients with documented or presumed HPA axis suppression. Prednisone (or equivalent) in a single morning dose of 5 mg does not cause clinically significant suppression of the HPA axis (42). Five published recommendations agree with our recommendations (33, 42, 48–50).

Our results bring out several controversies regarding the perioperative management of HRT and of non-steroidal anti-inflammatory drugs. Consequently, the result of the experts panel was not consensual. Therefore, additional investigation is required to support a practical recommendation.

Hormone replacement therapy

Extrapolated evidence form one cohort study (17) (evidence level 2^{++}) and from one case–control study (19) (evidence level 2^{+}) recommend continuation of HRT in the perioperative period with strength classification of C. However, the formal consensus panel defended withdrawal of HRT before surgery, because of higher risk of thromboembolism with this therapy compared with OC. Oestrogen dosages in HRT are higher and the target population is older. Moreover, suspension of HRT can reverse the symptoms of menopause but does not present the risk of unwanted pregnancy. On the other hand, the Portuguese clinical practice pre-operative consultation schedule does not allow withdrawal of HRT 4–6 weeks prior to surgery.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) have antiplatelet effects, leading to increased risk of surgical bleeding. Selective cyclo-oxygenase-2 inhibitors have minimal effects on platelet activity but, like other NSAIDs, have the potential for causing renal dysfunction (28, 30, 51). Thus, five published recommendations agree that NSAIDs should be withdrawn before surgery, according to their half-life (28, 30, 37, 40, 51). On the other hand, during the formal consensus meeting some experts argued that it does not make sense to withdraw

NSAIDs before surgery and after surgery then administer analgesics to control pain. Consequently, there was not agreement in the formal consensus.

As with any systematic review, this study has limitations. Although a comprehensive literature search was carried out, publication bias could be questioned due to language and publication year limits. However, the recommendations were developed on the basis of a number of different evidence sources and we believe that formal consensus was valuable and helpful clarifying some lack of evidence and contradictory findings.

Efforts were made to minimize bias by having two investigators independently undertake the study quality assessment and data extraction. Studies were relatively heterogeneous with respect to patient population, study design, treatment regimen and studied end-points. Knowing that the quality of a systematic review is always a reflection of the quality of included studies, our recommendations have limited strength of evidence (maximum evidence level C), but most of them agree with prior published recommendations.

The formal consensus panel comprised a multidisciplinary group with recognized expertise. However, only seven of the 11 specialists completed all rounds of the consensus process. A direct pre- and post-meeting comparison of the round ratings was not performed because some of the statements changed in their wording during the meeting in the light of clarifying comments of the participants.

WHAT IS NEW AND CONCLUSION

The formal consensus method implemented proved to be a practical and helpful method to integrate different strands of evidence for the development of evidence practice guidelines. Epidemiologic studies concerning the perioperative management of chronic medications are clinically heterogeneous and there are few randomized clinical trials available. Consequently, for some therapeutic groups, it was not possible to achieve consensus and define a practical recommendation.

Despite the limitations of this study, we believe that it makes an important contribution for the perioperative management of chronic medication and helps to clarify some of the rationale supporting each decision.

Nevertheless, further epidemiologic studies are needed to increase strength of evidence of the developed practice recommendations and to support the development of new recommendations.

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4.1.2 Artigo II

"Chronic Medication in the Perioperative Period – usage profile and risk management"

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A MEDICAÇÃO CRÓNICA NO PERÍODO PERIOPERATÓRIO
Perfil de Utilização e Gestão de Risco

Liliana CASTANHEIRA, Ana PALMEIRO, Paula FRESCO, Ana Filipa MACEDO

RESUMO

Introdução: Actualmente, um número crescente de cirurgias é realizado numa população cada vez mais idosa e de maior risco, devido à comorbilidade inerente e polimedicação associada neste grupo populacional. A identificação dos perfis de utilização da medicação crónica no período perioperatório é necessária para uma eficiente gestão do risco de iatrogenia.
Métodos: Durante um ano, todos os doentes com mais de 18 anos, admitidos para cirurgia geral, no Centro Hospitalar Cova da Beira, foram incluídos no estudo. Registaram-se os dados demográficos e toda a informação sobre a medicação crónica e a sua administração no período perioperatório nos doentes em estudo.
Resultados: No total, foram analisados dados relativos a 404 doentes. A maioria dos doentes (69,9%) toma medicação crónica (média de 2,5 medicamentos por doente), principalmente *antihipertensores* (58,5%) e *psicofármacos* (33,5%). Foram registados 973 medicamentos de utilização crónica, sendo que 79,1% foram suspensos antes da cirurgia, 10,7% foram continuados e 7,7% foram substituídos por um medicamento do mesmo grupo terapêutico durante o período de internamento.
Conclusões: A maioria dos doentes submetidos a cirurgia geral toma medicação crónica, sendo na maior parte dos casos suspensa antes da cirurgia. É necessário avaliar as complicações no período perioperatório, como consequência da suspensão dos medicamentos de utilização crónica, para uma melhor gestão da terapêutica cirúrgica.

SUMMARY

CHRONIC MEDICATION IN THE PERIOPERATIVE PERIOD
Usage profile and risk management

Introduction: Currently, an increasing number of surgeries are performed in an older and higher risk population, due to the inherent comorbidity and polypharmacy associated with this population group. The characterization of drug usage profiles in the perioperative period is critically needed to understand the nature of adverse events and to achieve a more efficient iatrogenic risk management.
Methods: During 1 year, all adult patients (>18 years) consecutively admitted for elective surgery at "Cova da Beira" Hospital Center (CHCB) were included in the study. The demographic characteristics, and data on chronic medication use and their administration to the patients in study, in the perioperative period were collected.
Results: A total of 404 patients were evaluated. The majority of patients (69.9%) were taking chronic medication (mean 2.5 by admission), mainly "anti-hypertensive" (58.5%) and "psychotropics" (33.5%). 973 drugs were registered as chronic medication. 79.1% of these drugs were withdrawn before the surgery, 10.7% were continued and 7.7% were replaced for another drug of the same therapeutic group.
Conclusions: The majority of patients, admitted for general surgery, take chronic medications, which were withdrawn before surgery, in the majority of cases. Additional assessment of perioperative complications, as result of drug withdrawal, is urgently needed for surgical therapeutic management.

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INTRODUÇÃO

Nos últimos anos, a evolução das técnicas cirúrgica e anestésica diminuíram a incidência de complicações pós-operatórias. Verificou-se um aumento da acessibilidade aos cuidados cirúrgicos e uma maior complexidade das patologias de intervenção. Consequentemente, um número crescente de cirurgias é realizado numa população cada vez mais idosa e de maior risco, devido à comorbilidade inerente e à polimedicação associada a este grupo populacional[1].

Segundo um estudo realizado por *Kennedy* et al[2], cerca de 50% dos doentes submetidos a procedimentos cirúrgicos fazem medicação crónica (média 2,4 ± 2,8), em 48% dos casos para patologia cardiovascular e 45% para patologia do sistema nervoso central. Estes doentes apresentam um risco acrescido de complicações pós-cirúrgicas (2,7; 95% IC 1,76-4,04), das quais 5% directamente atribuídas à suspensão da medicação.

A informação sobre a utilização de medicamentos no período perioperatório e o respectivo impacto no resultado cirúrgico é limitada. A prática clínica é, na maioria dos casos, empírica e inconsistente, dificultando a antecipação das consequências de cada decisão e a ponderação integrada benefício/risco em cuidados cirúrgicos. A identificação dos perfis de utilização da medicação crónica no período perioperatório é por isso o primeiro passo para melhorar o conhecimento da prática clínica, com vista à harmonização de procedimentos e uma mais eficiente gestão do risco iatrogénico em cuidados cirúrgicos. O objectivo deste estudo é caracterizar a utilização e a gestão da medicação crónica dos doentes admitidos durante um ano para cirurgia geral num Hospital Distrital Universitário.

POPULAÇÃO E MÉTODOS

Após aprovação do estudo pela Comissão de Ética do Centro Hospitalar Cova da Beira (CHCB), os doentes consecutivamente admitidos para cirurgia geral electiva foram recrutados na consulta de anestesia do CHCB. O estudo teve uma duração de 12 meses. Os critérios de inclusão foram os seguintes: doentes com idade superior a 18 anos e admitidos para cirurgia geral. Os doentes de cirurgia de ambulatório foram excluídos.

No período que antecedeu a consulta de anestesia foi aplicado um questionário a todos os doentes que, após consentimento informado, aceitaram participar no estudo. O questionário permitiu recolher os dados demográficos e de utilização de medicação crónica de cada doente.

Após a realização da cirurgia foram consultados, no arquivo do CHCB, os processos clínicos de cada doente, para confirmar os dados recolhidos antes da consulta de anestesia e registar a administração da medicação crónica no período perioperatório. Foi considerada crónica, a medicação que o doente tomava há mais de duas semanas antes da cirurgia.

Os dados recolhidos foram inseridos numa base de dados da Microsoft Access 2007, construída propositadamente para o estudo. Para a análise de dados utilizou-se o Microsoft Access 2007 e o *Statistical Package for the Social Sciences* (SPSS).

RESULTADOS

Caracterização da amostra e utilização de medicação crónica

A amostra incluiu 404 doentes, 46,5% mulheres e 53,5% homens, com idade média de 57 anos (intervalo 19-90). Dois doentes foram admitidos duas vezes para cirurgia geral electiva, contabilizando um total de 406 internamentos.

A maioria dos doentes (n = 284; 69,9%) tomava medicação crónica, registando-se um total 973 medicamentos, em média 2,5±2,8 medicamentos por doente, até um máximo de 14 medicamentos. Dos 284 doentes que faziam medicação crónica, 16,3% tomava um medicamento, 24,4% tomava dois a três medicamentos e 29,2% tomava quatro ou mais medicamentos. O quadro 1 apresenta a proporção de doentes que tomavam pelo menos um medicamento, do grupo terapêutico respectivo.

Os doentes tomavam principalmente *anti-hipertensores* (58,5%), *psicofármacos* (33,5%) e *insulina, antidiabéticos orais e glucagon* (30,6%). De referir ainda que 37,9% dos doentes a fazer *anti-hipertensores*, 39,0% dos doentes a fazer *psicofármacos* e 24,2% dos doentes a fazer *insulina,*

Quadro 1 – Proporção de medicamentos em utilização crónica pelos doentes, por grupo terapêutico

Grupo terapêutico	Doentes N (%)
Anti-hipertensores	166 (58,5)
Psicofármacos	95 (33,5)
Insulinas, antidiabéticos orais e glucagom	87 (30,6)
Antiácidos e anti-ulcerosos	79 (27,8)
Anticoagulantes e Antitrombóticos	66 (23,2)
Antidislipidémicos	60 (21,1)
Venotrópicos	38 (13,4)
Vasodilatadores	34 (11,3)
Hormonas sexuais	27 (9,5)
Antiasmáticos e Broncodilatadores	20 (7,0)
Antiepilépticos e Anticonvulsivantes	20 (7,0)
Outros medicamentos usados em disfunções geniturinárias	15 (5,3)
Hormonas da Tiróide e Antitiróideus	15 (5,3)

antidiabéticos orais e glucagon tomavam dois ou mais medicamentos desse grupo terapêutico.

Gestão da medicação crónica

No período perioperatório, 79,1% (n=770) dos medicamentos foram suspensos antes da cirurgia, 10,7% (n=104) foram continuados e 7,7% (n=75) foram substituídos por um medicamento do mesmo grupo terapêutico (Quadro 2).

A suspensão dos medicamentos foi feita sobretudo no dia (n=259; 26,6%) ou um dia antes da cirurgia (n=276; 28,4%). A mesma análise, de acordo com os diferentes grupos terapêuticos revelou que a decisão mais prevalente para todos os grupos terapêuticos foi a de suspensão do medicamento antes da cirurgia (Quadro 3).

Os *antidislipidémicos* e as *hormonas sexuais* foram suspensos em todos os doentes. Por outro lado, os *anticoagulantes e antitrombóticos* foram unicamente suspensos (81,4%) ou substituídos (18,6%). Os grupos terapêuticos das *insulinas, antidiabéticos orais e glucagom*, *antiácidos e anti-ulcerosos*, e *anticoagulantes e antitrombóticos* foram os que apresentaram maior proporção de substituição (18.9%; 28.6%; 18.6%, respectivamente). Os grupos terapêuticos das *hormonas da tiróide e antitiróideus*, *antiasmáticos e broncodilatadores*

Quadro 2 – *Gestão da Medicação Crónica no Período Perioperatório*

	N	%
Suspensão	**770**	**79,1**
Suspensão antes da cirurgia (não se sabe o dia)	162	16,6
Suspensão 4 ou mais dias antes da cirurgia	50	5,1
Suspensão 2 a 3 dias antes da cirurgia	23	2,4
Suspensão 1 dia antes da cirurgia	276	28,4
Suspensão no dia da cirurgia	259	26,6
Suspensão depois da cirurgia	24	2,5
Substituição	**75**	**7,7**
Continuação	**104**	**10,7**

Quadro 4 – *Tempos de suspensão dos diversos grupos terapêuticos*

Período de Suspensão	Grupo Terapêutico	Medicamentos Suspensos N (%)
≥2 dias antes da cirurgia	Anticoagulantes e Antitrombóticos	48 (84,2)
	Antidislipidémicos	2 (6,6)
1 dia antes da cirurgia	Psicofármacos	21 (46,6)
	Antihipertensores	21 (11,4)
	Antidislipidémicos	46 (75,4)
No dia da cirurgia	Psicofármacos	28 (27,2)
	Antihipertensores	123 (66,5)
	Antidislipidémicos	4 (3,3)

Quadro 5 - *Medicamentos Readministrados no pós-operatório, por grupo terapêutico*

Grupo Terapêutico	Readministração N (%)
Anti-hipertensores	30 (17,1)
Psicofármacos	21 (20,8)
Antiácidos e anti-ulcerosos	5 (9,1)
Anticoagulantes e antitrombóticos	2 (3,6)
Insulinas, antidiabéticos orais e glucagon	8 (34,8)
Vasodilatadores	5 (19,2)
Antiasmáticos e Broncodilatadores	5 (16,7)
Outros medicamentos usados em disfunções geniturinárias	4 (28,6)
Antiepilépticos e Anticonvulsivantes	3 (18,8)
Antidislipidémicos	2 (3,3)

Quadro 3 – *Gestão da Medicação Crónica no Período Perioperatório*

Grupo terapêutico	Continuação N (%)	Suspensão N(%)	Substituição N(%)
Anti-hipertensores	35 (15,0)	185 (79,1)	14 (6,0)
Psicofármacos	21 (15,3)	103 (75,2)	13 (9,5)
Insulinas, antidiabéticos orais e glucagom	5 (13,5)	25 (67,6)	7 (18,9)
Antiácidos e anti-ulcerosos	4 (4,8)	56 (66,7)	24 (28,6)
Anticoagulantes e Antitrombóticos	0 (0)	57 (81,4)	13 (18,6)
Antidislipidémicos	0 (0)	61 (100)	0 (0)
Venotrópicos	2 (5,3)	36 (94,7)	0 (0)
Vasodilatadores	4 (12,1)	28 (84,8)	1 (3)
Hormonas sexuais	0 (0)	25 (100)	0 (0)
Antiasmáticos e Broncodilatadores	9 (23,1)	30 (76,9)	0 (0)
Antiepilépticos e Anticonvulsivantes	13 (21,3)	46 (75,4)	2 (3,3)
Outros medicamentos usados em disfunções geniturinárias	2 (11,8)	15 (88,2)	0 (0)
Hormonas da Tiróide e Antitiróideus	4 (28,6)	10 (71,4)	0 (0)

e *antiepilépticos e anticonvulsivantes* foram os que apresentaram maior proporção de continuação terapêutica no perioperatório (28.6%; 23.1%; 21.3%, respectivamente). Considerando os principais grupos terapêuticos suspensos num maior número de doentes (*anti-hipertensores*, *psicofármacos*, *antidislipidémicos* e *anticoagulantes e antitrombóticos*), a suspensão ocorreu principalmente um dia antes da cirurgia ou no dia da cirurgia no para os *psicofármacos*, dos *anti-hipertensores*, um dia antes da cirurgia para os *antidislipidémicos* e dois ou mais dias antes da cirurgia para os *anticoagulantes e antitrombóticos* (Quadro 4).

Dos 770 medicamentos suspensos antes da cirurgia, 94 (12.2%) foram readministrados no pós-operatório. No quadro 5 é apresentada a proporção de medicamentos que foram readministrados no pós-operatório, depois de terem sido suspensos antes da cirurgia, por grupo terapêutico.

Dos 175 anti-hipertensores suspensos antes da cirurgia e que não foram substituídos, 17.1% foram readministrados no pós-operatório. Dos 101 *psicofármacos* suspensos antes da cirurgia e que não foram substituídos, 20.8% foram readministrados no pós-operatório. Os medicamentos pertencentes aos grupos terapêuticos *insulinas, antidiabéticos orais e glucagon* e *outros medicamentos usados em disfunções geniturinárias* foram os que apresentaram maior proporção de readministração (34.8% e 28.6%, respectivamente), após a sua suspensão no pré-operatório.

Uma vez que os *anti-hipertensores* e os *psicofármacos* foram os mais utilizados e com elevada proporção de suspensão, analisou-se novamente a suspensão *vs* a continuação por classe farmacológica, com intuito de compreender se os fármacos que foram suspensos são diferentes dos que foram continuados (Figura 1 e 2). Nesta análise foram incluídos apenas os medicamentos suspensos antes da cirurgia e os que foram continuados, excluíndo os medicamentos que foram suspensos depois da cirurgia e os que foram substituídos.

Através da análise da figura 1, é possível constatar que a decisão mais frequente em todas as classes de *anti-hipertensores* foi a de suspender o medicamento antes da cirurgia. Contudo, em todas classes há uma proporção de doentes que continuaram a medicação, sendo esta decisão mais frequente na classe dos diuréticos (30%) e menos frequente na classe dos inibidores da enzima de conversão da angiotensina (IECAS) e aos antangonistas

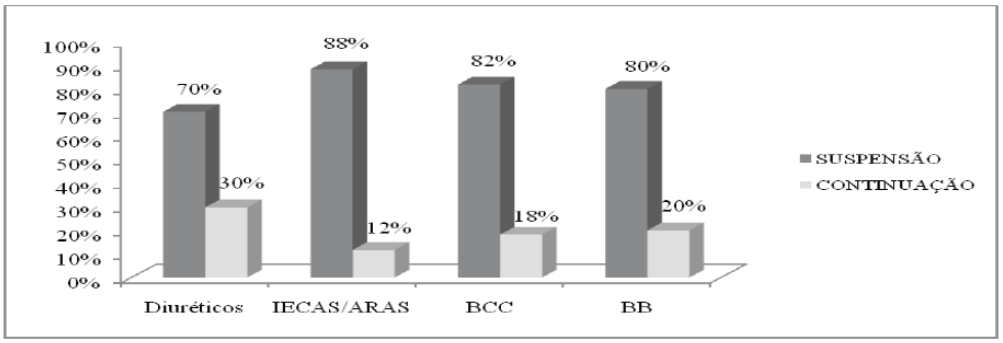

Fig. 1 – Suspensão *vs* Continuação das diferentes de classes de Anti-Hipertensores (ARAS-Antagonistas dos receptores da angiotensina; BB-Beta bloqueadores; BCC-Bloqueadores dos canais de cálcio; IECAS-Inibidores da enzima de conversão da angiotensina.)

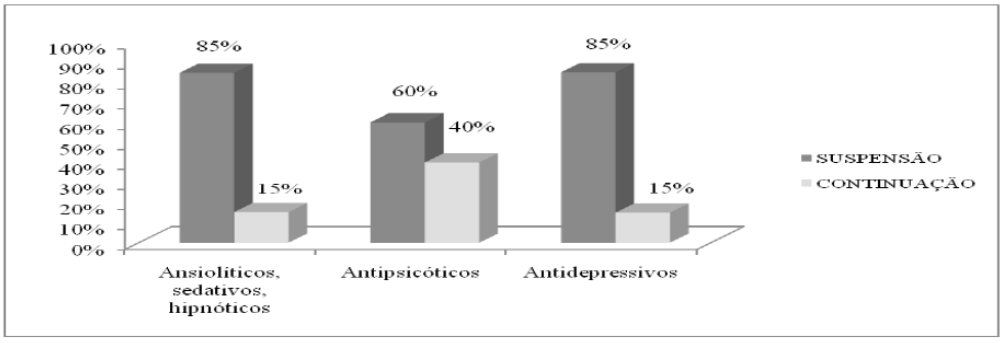

Figura 2 – Suspensão *vs* Continuação das diferentes de classes de Psicofármacos

dos receptores da angiotensina (ARAS) (12%).

Através da análise da figura 2, é possível constatar que a decisão mais frequente em todas as classes de *psicofármacos* foi a de suspender o medicamento antes da cirurgia. No entanto, o número de antipsicóticos que são continuados (40%) não é muito inferior ao número dos que são suspensos (60%).

DISCUSSÃO

A caracterização da utilização de medicação crónica nos doentes admitidos para cirurgia geral e a sua gestão no período perioperatório são fundamentais para melhorar o conhecimento da prática clínica em Portugal, com vista à harmonização de procedimentos e eficiente gestão do risco iatrogénico em cuidados cirúrgicos.

Os doentes admitidos para cirurgia geral no CHCB fazem medicação crónica em 69.9% dos casos, sobretudo *anti-hipertensores* (58.5%), *psicofármacos* (33.5%), *insulinas, antidiabéticos orais e glucagom* (30.6%) e *antiácidos e anti-ulcerosos* (27.8%). Estes resultados estão de acordo com o estudo efectuado por *Kennedy* et al[2].

A maioria dos medicamentos em utilização crónica são suspensos antes da cirurgia (79.1%), dos quais 12.2% são reiniciados no pós-operatório. Apenas 10.7% dos medicamentos em utilização crónica são continuados e 7.7% são substituídos por outros medicamentos do mesmo grupo terapêutico, no período perioperatório. A pequena percentagem de reiniciação da medicação pode estar relacionada com o facto de a maioria dos doentes submetidos a cirurgia geral terem alta no dia à seguir à cirurgia, reiniciando a medicação crónica em casa.

Os grupos terapêuticos das *hormonas da tiróide* e *antitiróideus*, *antiasmáticos* e *broncodilatadores* e *antiepilépticos e anticonvulsivantes* foram os que apresentaram maior proporção de continuação terapêutica no perioperatório (28.6%; 23.1%; 21.3%, respectivamente).

Os *antidislipidémicos* (estatinas e fibratos) foram suspensos em todos os doentes. Devido ao risco de miopatia e rabdomiólise, os fibratos devem ser supensos antes da cirurgia[12]. Contudo, o *American College of Cardiology/ American Heart Association* recomenda a continuação de estatinas no perído perioperatório, pois alguns estudos verificaram que isso diminui o risco complicações vasculares[3,18].

Os anticoagulantes e antitrombóticos foram principalmente suspensos (81.4%), ou então substituídos (18.6%). Estes resultados estão de acordo com as recomendações clínicas do *American College of Chest Physicians*, de suspensão dos anticoagulantes e antitrombóticos, ou substituição por heparinas de baixo peso molecular, quando o doente apresenta um risco moderado ou elevado de tromboembolismo[17].

Os medicamentos pertencentes ao grupo terapêutico *insulinas, antidiabéticos orais e glucagom* foram substituídos (18.9%) ou suspensos, seguidos de readministração (34.8%), o que é justificado pela importância do controlo da glicemia no período perioperatório. A decisão de substituir ou suspender com ou sem readministração não é uniforme, porque está dependente das características do doente e da cirurgia. Por exemplo, um diabético de tipo 1 poderá não suportar um período de jejum prolongado e entrar em cetoacidose se não tiver um aporte insulínico suficiente; já um diabético de tipo 2 poderá ser muito menos sensível à insulina administrada, necessitando de quantidades maiores, mas geralmente suportará o jejum com mais facilidade, desde que se mantenha bem hidratado[16].

Em relação aos *anti-hipertensores*, em todas as classes de a decisão mais frequente foi suspender o medicamento antes da cirurgia (80%). No entanto, relativamente aos beta bloqueadores (BB), esta decisão não está de acordo com a recomendação do *American College of Cardiology/ American Heart Association* que recomenda a continuação dos BB durante o período perioperatório[3]. Isto porque está demonstrado que a suspensão dos BB no período perioperatório aumenta o risco de morbilidade e mortalidade no período pós-operatório[4,5]. Relativamente, aos IECAS/ ARAS não existe um consenso sobre qual é a melhor opção. Diferentes estudos demonstraram que continuar os IECAS/ ARAS até ao dia da cirurgia aumenta a incidência de episódios de hipotensão, contudo reduz a possibilidade de ocorrência de hipertensão no pós-operatório[6-9]. Alguns autores recomendam mesmo continuar os IECAS no período perioperatório, para prevenir episódios de hipertensão no pós-operatório[10-12]. Os nossos resultados reflectem esta controvérsia (88% *vs* 12%).

No caso dos diuréticos, não existe nenhum estudo que compare a suspensão com a continuação no período perioperatório, e também não existe nenhum consenso sobre qual a melhor opção. A administração de diuréticos na manhã da cirurgia pode aumentar o risco de hipotensão durante a cirurgia, por outro lado durante a cirurgia podem administrar-se diuréticos caso seja necessário. Desta forma, existem vários autores que recomendam a suspensão na manhã da cirurgia[12-15], sendo esta a opção mais frequentemente tomada no nosso estudo (70%). Relativamente aos bloqueadores dos canais de cálcio (BCC), também não existem estudos que comparem a suspensão com a continuação no período perioperatório. No entanto, as recomendações ditam a continuação dos BCC para a manutenção de estabilidade hemodinâmica[12,14]. No

nosso estudo, esta recomendação não é seguida na maioria (82%) dos doentes.

No grupo terapêutico dos *psicofármacos*, a decisão mais frequente também foi suspender a medicação antes da cirurgia. Estes resultados contrariam as recomendações publicadas[12,14]. Para as três classes de psicofármacos as recomendações são para continuar a medicação no perioperatório, principalmente nos doentes com patologia mais severa, tendo em atenção a possível interacção com fármacos utilizados na anestesia[12,14].

CONCLUSÃO

Concluimos assim que a gestão da medicação crónica no período perioperatório, para alguns medicamentos, não segue as recomendações definidas pela comunidade científica. São necessários estudos adicionais para conhecer o impacto destas decisões clínicas no resultado cirúrgico e/ou possíveis complicações pós-operatórias, e assim desenvolver recomendações para a gestão do risco iatrogénico em cuidados cirúrgicos.

Apesar de a recolha de dados ter sido retrospectiva, e por isso limitada pela qualidade dos registos, não condicionou de forma expressiva os resultados obtidos, pois apesar de em 16% dos medicamentos não se saber exatamente o dia da suspensão, foi registada a decisão de suspensão. Este estudo permite caracterizar a utilização da medicação crónica, durante um ano, no serviço de cirurgia geral de um hospital distrital universitário e a sua gestão no periodo perioperatório,constituindo por isso um importante contributo para a melhorar o conhecimento da prática clínica, com vista ao desenvolvimento e implementação de recomendações, fundamentais para a utilização mais segura de medicamentos em cuidados cirúrgicos.

Conflito de interesses:

Os autores declaram não ter nenhum conflito de interesses relativamente ao presente artigo

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4.2.1 Artigo III

"Chronic utilization of agents acting on the renin-angiotensin system and intraoperative arterial pressure."

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Chronic utilization of agents acting on the renin-angiotensin system and intraoperative arterial pressure

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Abstract. – BACKGROUND, There has been concern that taking agents acting on the renin-angiotensin system (ARAS) in surgery day, may predispose patients to higher risk of intraoperative hypotension during surgery. Therefore, the European Society of Cardiology and the European Society of Anesthesiology recommend transient discontinuation of ARAS before non-cardiac surgery in hypertensive patients. As the existent evidence is limited, this recommendation remains debated.

AIM, The objectives of the study were to evaluate the effects of ARAS chronic utilization on intraoperative arterial pressure.

PATIENTS AND METHODS, This historical cohort consisted in recruitment of surgery patients over 12 months, at "Cova da Beira Hospital Center. The data were gathered from an interview to the patient and by postoperative review of the medical record.

RESULTS, The study consisted of 756 patients. Of those, 589 did not take antihypertensive medication and 176 were taking chronic ARAS.

In univariate analysis, only the appearance of intraoperative hypertension was significantly greater in ARAS group. In logistic regression analysis, age, diabetes and taking ARAS were the only significant risk factors to the appearance of intraoperative hypertension.

In ARAS group, 123 patients stopped the ARA before surgery and 53 continued it until the surgery day. The frequency of the two outcomes did not differ between the two groups.

CONCLUSIONS, In our study hypotension episodes during non-cardiac surgery could not be attributed to ARAS chronic utilization and taking ARAS on surgery morning when compared with withdrawal was not associated with hypotension episodes.

Key Words:
Angiotensin-converting enzyme inhibitors, Angiotensin II antagonists, Intraoperative arterial pressure, Surgery.

Introduction

Agents acting on renin-angiotensin system (ARAS) are established as safe and effective therapeutic in hypertension, namely in patients with concomitant diabetes or compromised left ventricular function[1]. As result a large proportion of patients presenting for elective surgery are taking ARAS to treat some form of cardiovascular diseases. Several reports suggest that taking ARAS in surgery day may predispose patients to higher risk of intraoperative hypotension during surgery[2-6]. Intraoperative hypotension has been associated with postoperative cardiovascular events, renal dysfunction and mortality[7-12]. Therefore, the European Society of Cardiology and the European Society of Anesthesiology recommend transient discontinuation of ARAS before non-cardiac surgery in hypertensive patients[13]. As there is limited evidence and some data suggest this recommendation may result in hypertension in the postoperative period, this subject remains debated[14]. However, the same guidelines recommend that ARAS be continued during non-cardiac surgery in stable patients with left ventricular systolic dysfunction. Further perioperative studies are critically needed to evaluate the effects of ARAS chronic utilization in arterial pressure.

The objectives of the study were to evaluate the effects of chronic utilization of ARAS on arterial pressure during the operative period.

Patients and Methods

This historical cohort was approved by the Ethics Committee of Cova da Beira Hospital Center (CBHC) that provided a written consent, to be requested to each patient. The written con-

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sent was presented to the patient before the interview. The records of patients that refused to participate in study could not be consulted. Therefore, only the patients that gave written consent were included in the study.

Patients were selected over 12 months, between September 2008 and September 2009 at CBHC. Eligible patients included those having at least 18 years old, an anesthesia consultation, proposed for elective general, orthopedic, gynecologic, urologic, neurologic, maxillofacial, ear, nose and throat (ENT) and plastic surgery. The exclusion criteria were ambulatory surgery, local anaesthesia, patients taking other cardiovascular drugs than ARAS, not speaking portuguese or any condition that compromised patients ability to communicate and/or understanding and the absence of written consent.

Patients were interviewed before anesthesia consultation by a member of the research team, to ensure that criteria for enrollment were met and to query regarding chronic medication. Chronic medication was defined as the medication which the patient was taking for more than 2 weeks before the surgery.

All other data were gathered from postoperative review of the medical record. Three separate sets of data were collected: demographic characteristics, chronic medication use, the clinical information.

The patient demographics and chronic medication use was asked in the interview and confirmed in medical record. These include the age, sex, weight, and height, the name of each chronic medication, route administration and stop and start dates.

The clinical information included the American Society of Anaesthesiologists physical status classification (ASA), surgery service, occupation time in surgery, type of anaesthesia and drugs given in perioperative period. Clinical history data (previous surgeries, chronic diseases) and exam pre-operatory results were not possible to access due to administrative restrictions. As such it was not possible to separate patients taking ARAS for hypertension from those taking them because of left ventricular systolic dysfunction.

The outcomes hypertension and hypotension were defined by threshold values with concomitant administration of antihypertensives or vasopressors drugs. The limit threshold was systolic blood pressure value more than 160 mm Hg for hypertension, and systolic blood pressure value less than 85 mm Hg for hypotension.

In the analysis, first we compared patients that take no antihypertensive medication with patients on ARAS. Antihypertensive medication includes diuretics, beta blocking agents, calcium channel blockers, antiadrenergic agents and ARAS. The ARAS includes angiotensin-converting enzyme inhibitors in plain (the pill only had the angiotensin-converting enzyme inhibitor) and in combination (the pill had two drugs, the angiotensin-converting enzyme inhibitor and a diuretic or a calcium channel blockers), angiotensin II antagonists in plain and in combination (diuretics or calcium channel blockers). In a second approach, the group of patients on chronic ARAS were divided in two, patients that withdrawal ARAS in the days before or in the surgery day (ARAS stop group) and the group that took ARAS until the day of surgery (ARAS continue group), inclusively (this includes the patients in which ARAS were replaced for a drug of the same subtherapeutic group).

On the basis of a previous report[4], it was assumed that 67% ARAS continue group would have at least one hypotension episode during surgery. To detect a 30% difference in frequency of hypotension episode during surgery between ARAS continue group versus ARAS stop group, with a power of 80% (two tailed $\alpha = 0.05$), the sample size should have a minimum of 25 patients per group.

The continuous variables were initially assessed for normality. Variables found to be normally distributed were compared using Student *t*-test, while non-normally distributed variables were compared using Mann-Whitney U tests. Categorical variables were compared using chi-square tests. All associations found to be significant in the univariate analysis ($p < 0.05$) were entered into a forward stepwise logistic regression analysis to identify predictors of outcomes. A p value cutoff of 0.05 for entry and 0.10 for exit was used. Results from the multivariate model have been reported as Odd's Ratios (OR) with 95% Confidence Interval (CI). A two-sided p value of 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS Version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

The study consisted of 765 patients. Of those, 589 did not take antihypertensive medication and 176 were taking chronic ARAS (Figure 1).

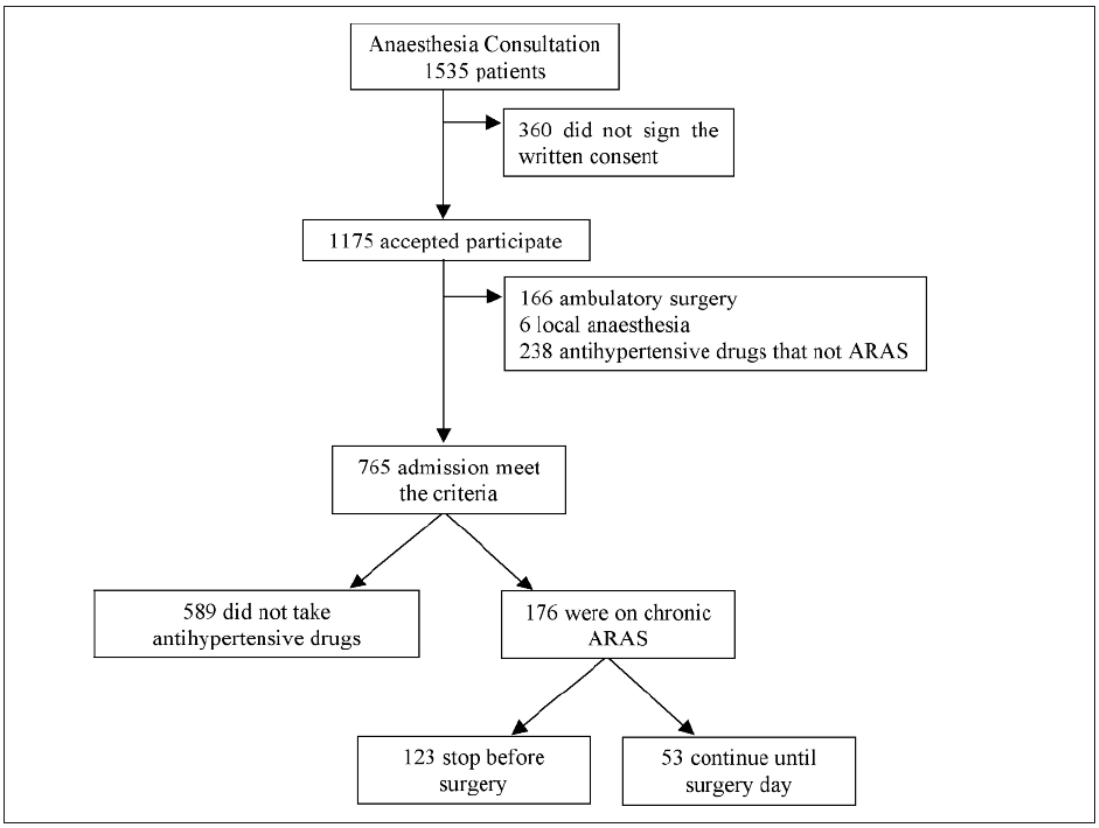

Figure 1. Flow diagram of the patients enrolled in the study.

The medical records had some missing data, namely 15.7% did not have ASA status classification, 0.8% did not have type of anaesthesia, in 5.0% the occupation time was not registered and 0.7% did not have the day in which ARAS were suspended.

In groups, (no antihypertensive medication and chronic ARAS) there were more female patients. Chronic ARAS group had a mean age of 13 years older and more patients with diabetes requiring therapy. As in the distribution of patients in the ASA status classification it is not possible to apply Chi-square test, we decided to aggregate ASA I with ASA II (ASA I/II) and ASA III with ASA IV (ASA III/IV). Chronic ARAS group had more patients with ASA III/IV classification ($p = 0.000$). The number of patients submitted to general or regional anaesthesia was similar in the two groups. In chronic ARAS group there is a higher proportion having surgery more than 121 minutes with a statistically significant difference ($p = 0.020$) (Table I).

There was an increased frequency of the two outcomes evaluated in Chronic ARAS group. However, in univariate analysis, only the frequency of intraoperative hypertension was significantly greater in chronic ARAS group (Table I). In logistic regression analysis of the risk factors to appearance of intraoperative hypertension, only age ($p = 0.000$, OR 1.05, 95% CI 1.03-1.08), diabetes ($p = 0.034$, OR 2.45, 95% CI 1.07-5.60) and chronic ARAS use ($p = 0.038$, OR 1.91, 95% CI 1.04-3.50) were statistically significant. The ASA status ($p = 0.283$) and the occupation time ($p = 0.290$) were not associated to intraoperative hypertension in logistic regression.

In chronic ARAS group, 123 (77.4%) patients stopped ARAS before surgery and 53 (30.1%) continue the medication until surgery day, inclusively. The two groups were comparable in patient characteristics (Table II). The frequency of the two outcomes did not differ between the two groups.

The appearance of hypertension was significantly higher in ARAS stop group ($p = 0.000$)

Table I. Patient characteristics by groups no antihypertensive medication and chronic ARAS

Characteristic	Patients number (%)		
	No antihypertensive medication (n = 563)	Chronic ARAS (n = 176)	χ^2 (p)
Sex			
Female	373 (63.3)	118 (67.0)	0.367
Male	216 (36.7)	58 (33.0)	
Age (years)			
Mean (standard deviation)	49.58 (14.76)	62.95 (11.11)	0.000
Diabetes requiring theraphy	19 (3.2)	27 (15.3)	0.000
ASA Status			
I/II	449 (91.1)	114 (75.0)	0.000
III/IV	44 (8.9)	38 (25.0)	
Type of Anesthesia			
General	468 (80.1)	139 (79.4)	0.837
Regional	116 (19.9)	36 (20.6)	
Occupation Time (minutes)			
1-120	365 (64.8)	90 (54.9)	0.020
≥ 121	198 (35.2)	74 (45.1)	
Outcomes			
Hypertension	38 (6.5)	35 (19.9)	0.000
Hypotension	34 (5.8)	14 (8.0)	0.295

and ARAS continue group (p = 0.001), when compared with no antihypertensive medication group. Nevertheless the frequency of hypotension was similar between no antihypertensive medication and chronic ARAS either continuing (p = 0.544) or stopping it (p = 0.323).

Of the 123 patients that withdrawal the medication, 96 (78.0%) stopped in the surgery day, 21 (17.0%) stopped one day before de surgery, 3 (2.4%) stopped two or more days before the surgery and data is missing in 3 (2.4%) patients. There was no difference in the frequency of two

Table II. Patients characteristics by chronic ARAS management

Characteristic	ARAS – number of patients (%)		
	Stop (n = 123)	Continue (n = 53)	χ^2 (p)
Sex			
Female	77 (62.6)	41 (77.4)	0.056
Male	46 (37.4)	12 (22.6)	
Age (years)			
Mean (standard deviation)	3.07 (11.89)	62.70 (9.150)	0.825
Diabetes requiring therapy	18 (14.6)	9 (17.0)	0.692
ASA Status			
I/II	82 (75.9)	32 (72.7)	0.680
III/IV	26 (24.1)	12 (27.3)	
Type of Anesthesia			
General	98 (80.3)	41 (77.4)	0.655
Regional	24 (19.7)	12 (22.6)	
Occupation Time (minutes)			
1-120	59 (52.7)	31 (59.6)	0.406
≥ 121	53 (47.3)	21 (40.4)	
ARAS Classes			
ARAS in plain	57 (67.9)	27 (32.1)	0.575
ARAS in combination	66 (71.7)	26 (28.3)	
Cardiac Adverse Event			
Hypertension	24 (19.5)	11 (20.8)	0.850
Hypotension	10 (8.1)	4 (7.5)	1.000

outcomes between patients who withdrawn ARAS in surgery day and patients that stopped ARAS one or more days before surgery (Table III).

Discussion

There has been concern that taking ARAS in surgery day may predispose patients to higher risk of intraoperative hypotension during non cardiac surgery. The present study found no evidence to support this risk.

In the present study patients taking ARAS had more risk of intraoperative hypertension, than the patients taking no antihypertensive medication, when adjusted to confounders. This result can be expected, because ARAS are a therapy of choice in hypertensive disease. However, there is no difference in the occurrence of intraoperative hypotension between the two groups.

There was no statistically significant difference in the frequency of hypertension and hypotension between withdrawing and continuing chronic ARAS in perioperative period. Also, there was no significant difference in the occurrence of the two outcomes between patients that stop medication in surgery day and patients that stop the medication one or more days before surgery.

The patients that were taking beta-blockers and antiadrenergics drugs were excluded from the study, because beta-blockers may predispose patients to higher risk of intraoperative hypotension[15-16].

The management of the different antihypertensive drugs was not equal in all patients, which is an additional confounder. For this reason only the patients taking ARAS in combination (the same pill had the two drugs) were included in study. We not restrict the study to the patients that were taking only ARAS in plain, because the majority of patients (52.3%) were taking ARAS in combination.

Existing studies comparing ARAS users with ARAS non users, concluded that the number of patients requiring vasopressor was not significant different between the two groups[15,17]. In one study, the patients took ARAS in surgery morning and in the other patients did not take the ARAS in surgery morning[15,17]. These results are consistent with ours, although they did not exclude patients taking beta-blockers. However, a meta-analysis suggested that patients receiving an immediate preoperative ARAS were more likely (relative risk 1.50, 95% CI 1.15-1.96) to develop hypotension requiring vasopressors[18]. This meta-analysis is composed by five small studies with a considerable variation in design quality from study to study and it should be noted that the lower limit of 95% confidence interval for the OR approached 1, indicating that this was not a pronounced effect.

The lack of difference between the groups taking no antihypertensive medication and taking ARAS and between the groups withdrawing vs continuing chronic ARAS in risk of intraoperative hypotension is biologically plausible. The potent hypotensive effects of anesthetic, intraoperative analgesic agents and the surgery predominate relatively to the administration of ARAS.

The present study has several limitations. First, the data were collected as part of the medical record, not a specific study protocol data collection process. As such it was not possible to evaluate the indication (hypertension or left ventricular systolic dysfunction) for which ARAS were prescribed. We had some missing data and it is possible that some vasopressor bolus administered were not registered. Moreover, as the threshold for treatment of hypotension was not standardized by protocol, we may have underestimated the frequency of hypotensive episodes in this study. Also, some anesthesiologists use vasopressor or fluid boluses before hypotension occurs, which can further decrease the frequency of hypotension[6].

The European Society of Cardiology and the European Society of Anaesthesiology recommend transient discontinuation of ARAS before non-cardiac surgery in hypertensive patients, to reduce the risk of severe hypotension under anesthesia associated to perioperative use of ARAS. However, the same guidelines recommend their maintenance during non-cardiac

Table III. Outcomes by ARAS suspension day.

	Suspension day – number of patients (%)		
	Day surgery	≥ 1 day before surgery	χ^2 (p)
Hypertension	20 (20.8)	4 (16.7)	0.780
Hypotension	8 (8.3)	1 (4.2)	0.685

surgery in stable patients with left ventricular systolic dysfunction[13]. As ARAS preserve organ function and may prevent events related to myocardial ischemia and left ventricular dysfunction, independently of the blood pressure lowering effect, further larger scale prospective studies are critically needed to support ARAS discontinuation in hypertensive patients before surgery.

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4.2.2 Artigo IV

"Perioperative Chronic Medication Management"

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Perioperative Chronic Medication Management

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***SUMMARY*. The majority of patients submitted to surgical procedures are on chronic medication. Unfortunately, there are few outcome data about the majority of medications taken in the perioperative period and how clinicians manage chronic medication in this setting. All adult patients consecutively admitted for elective surgery at "Cova da Beira" Hospital Center were selected for the study. The study consisted of 929 patients submitted to elective surgery between September 2008 and July 2010. A total of 71.3 % were on chronic medication. The mean number of drugs taken was 2.4 ± 2.5(1-14). In logistic regression analysis both taking chronic medication and withdrawing it were not risk factors for the occurrence of adverse events.This work provides evidence that chronic medication and its management, either continuing or the withdrawal of it, may not add significant risk to perioperative period.**

INTRODUCTION

The volume of surgery is vast worldwide and the number of interventions performed is increasing due to advances in anaesthetic and surgical techniques, in a progressively elderly population and with multiple pathologies [1]. Many of these patients take chronic medication, which often improves their general well being at presentation for surgery. Kennedy *et al.* [2] found that half of the general surgical patients take medications unrelated to surgery and that taking a drug unrelated to surgery was associated with an increased relative risk of a postoperative complication by 2.7, compared with not taking any drug [2]. Of those patients, 5 % suffered postoperative complications directly attributable to withdrawal of their chronic medication.

Clinicians often must decide if chronic medications should be continued or withdrawn in the perioperative period. Unfortunately, there are few outcome data about the most frequent therapeutic groups of chronic medications taken in the perioperative period and how clinicians manage them. Also, there is a lack of evidence quantifying the risk of withdrawing or continuing of chronic medication during the perioperative period. It is necessary to evaluate the implications of chronic medication management in perioperative adverse events.

This retrospective study aimed to: identify the chronic medication use profile of a surgical population; quantify the relative importance of taking chronic medication and the impact of its perioperative management in the incidence of adverse events.

METHODS

This retrospective study was approved by the Cova da Beira Hospital Center (CBHC) Ethics Committee and written consent was requested from each patient. The records of patients that refused to participate in study could not be consulted. Therefore, only the patients

KEY WORDS: Adverse event, Chronic medication, Perioperative period.

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that gave written consent were recruited for the study.

Patients were recruited over 12 months, between September 2008 and September 2009, at CBHC. Eligible patients included those having at least 18 years old, an anaesthesia consultation and proposed for elective general, orthopaedic, gynaecologic, urologic, neurologic, maxillofacial, ear, nose and throat (ENT), plastic surgery. The exclusion criteria were ambulatory surgery, not speaking portuguese or any condition that compromised patients ability to communicate and/or understanding and the absence of written consent.

Patients were interviewed before anaesthesia consultation by a member of the research team to ensure that enrollment criteria were met and to query regarding chronic medication. Chronic medication was defined as medication the patient was taking for more than 2 weeks before surgery.

All other data were gathered from postoperative review of the medical record and from the Alert® report of urgency episodes within 30 days after discharge. This report was consulted in hospital computer system for each patient submitted to surgery. We decided to include these data because literature considers adverse events (AE) in this period can be potentially related to surgery or anesthesia [3,4].

For this study, the perioperative period was considered the entire length of stay. Five separate sets of data were collected: demographic characteristics, chronic medication use, the clinical information and adverse events (intraoperative, postoperative and 30 days after discharge).

The patient demographics and chronic medication use was asked in the interview and confirmed in medical record. These include the age, sex, weight, and height, the name of each chronic medication, administration route and stop and start dates.

The clinical information included the ASA classification, presenting pathology, the duration of the operative procedure (occupation time), type of anaesthesia, drugs given in perioperative period, including those administered in surgery and in hospitalization period. Clinical history data (previous surgeries, chronic diseases) and pre-operative exam results were not accessible due to administrative restrictions.

For the analysis of chronic medication, the anatomical therapeutic chemical (ATC) classification system was used. In the analysis of chronic medication management, patients were divided into 3 groups, the group that was not taking any medication, the group which stopped their chronic medication (this includes patients who had withdrawn at least one of their chronic medication) and the group that continued their chronic medication in perioperative period (this includes the patients that continued all their chronic medication or their chronic medication was replaced for a drug of the same subtherapeutic group).

The intraoperative AE (i.e. those occurring in the operating room), postoperative AE (i.e. those occurring during the patient's stay in the hospital after the surgery) and 30 days after discharge AE were defined as an injury related to medical management, in contrast to complications of disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care. The classification and examples of specific adverse events were presented in Table 1 for intra- and postoperative and 30 days after discharge AE. However, the intra- and postoperative AE advanced cancer death, fistula, anastomotic leak, urinary tract infection and all AE classified in other were excluded from the statistical analysis, because there is a lack of potential causal relation between these and chronic medication. Regarding AE within 30 days after discharge, only hypertensive crisis, gastrointestinal bleeding, anemia, deep vein thrombosis, hematoma, phlebitis, hemorrhage and edema were analysed together with other AE potentially related to chronic medication.

The continuous variables were initially assessed for normality. Variables found to be normally distributed were compared using Student t-tests, while non-normally distributed variables were compared using Mann-Whitney U tests. Categorical variables were compared using chi-square tests. The multivariate model was constructed using enter procedure. Results from the multivariate model have been reported as Odds Ratios (OR) with 95 % Confidence Interval (CI). A two-sided p-value of 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS Version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

At the pre-surgery evaluation systematically conducted by the anaesthesiologist, 1461 patients were eligible to participate in the study according to the inclusion criteria. Of those,

Categories	Adverse Event	
	Intra- and Postoperative	**30 Days after Discharge**
Death	Respiratory, advanced cancer death	-
Cardiovascular System	Arrythmia, hypertension, hypotension	Hypertensive crisis
Gastrointestinal System	Diarrhea, constipation, fistula, anastomotic leak	Nausea, vomiting, gastrointestinal bleeding
Genitourinary System	Urinary retention, oliguria/renal failure, urinary tract infection	Urinary retention, dysuria, infection, candidiasis, vaginal bleeding
Haematologic or Vascular System	Anemia, hemorrhage	Anemia, deep vein thrombosis, hematoma, phlebitis, hemorrhage
Wound	Infection, hematoma, dehiscense	Infection, dehiscence, inflammatory signs
Metabolic/Endocrine System	Hyperglycemia	-
Central Nervous System	Confusion, depression, psychiatric disorder unspecified	-
Pulmonary System	Aspiration, respiratory distress/ failure, pleural effusion	Pneumonia, infection
Other	Allergic reaction, anesthetic complication, medication error/toxicity, re-operation	Pain syndrome, dizziness, edema, post-dural puncture headache, fever, tonsillitis

Table 1. Specific Adverse Events by Categories.

24.6 % patients refused to participate in the study. Of the remaining 1102 patients, 173 were excluded because they were proposed for ambulatory surgery, or information about the surgery was lacking in medical records. These medical records were revised regularly during one year after the initial evaluation.

The study consisted of 929 patients admitted to elective surgery occurring between September 2008 and July 2010. There were 588 (63.3 %) female patients and 341 (36.7 %) male patients, with a mean age of 56 years old (range 20 to 92 years old). Of the 929 patients, 16.8 % were ASA I, 53.1 % were ASA II, 13.8 % were ASA III and 0.5 % were ASA IV. The majority of patients stayed in hospital two (46.2 %) or three days (24.3 %). The average day stay was 4.1 days (range 1 to 70 days) and the older the age group, the longer was the average day stay in the hospital. Almost 85 % of patients underwent general (44.7 %), gynaecological (30.4 %) and orthopaedic (9.6 %) surgery. 77.5 % of the patients underwent general anaesthesia. The average occupation time in operating room was 121 min (range 6-605 min). The medical records had missing data, namely 15.8 % did not have ASA status classification, 1.2 % did not have information about type of anaesthesia and 5.2 % did not have registered the occupation time.

A total of 71.3 % of patients admitted to surgery were taking chronic medication. The mean number of these drugs was 2.4 ± 2.5(range 1-14), which increased with age. Table 2 presents the number of patients by ATC groups of chronic medication. Of the 662 patients taking chronic medication, 62.1 % were on drugs for cardiovascular system, 55.9 % of those were taking two or more of this type of drugs (range 1-7). In addition, 40.9 % were taking nervous system drugs. The other large group comprises chronic medication for alimentary tract and metabolism (22.5 %). In perioperative period, 89.9 % of patients withdrawn their chronic medication. In the two main drug groups, 82.2 % of those on cardiovascular drug and 77.1 % on nervous system group, withdrawn their chronic medication.

On 929 patients, there were 2078 drugs of chronic use registered. Of those, 37.8 % were cardiovascular system drugs and 25.0 % were nervous system drugs (Table 3). Most drugs were withdrawn in perioperative period in all groups of chronic medication, with the exception of systemic hormonal preparations. This last referred group, included 47 drugs, 41 of which were thyroid therapy and six were corticosteroids. The thyroid therapy was continued in 25 patients, withdrawal in surgery day in 10 pa-

Anatomical Main Group	No. (%)
Cardiovascular System	411 (62.1)
Nervous System	271 (40.9)
Alimentary Tract And Metabolism	149 (22.5)
Blood and Blood Forming Organs	142 (21.5)
Genito Urinary System and Sex Hormones	132 (19.9)
Systemic Hormonal Preparations, excluding sex hormones and insulin	46 (6.9)
Respiratory System	40 (6.0)

Table 2. Number of Patients (No.) that take Chronic Medication by Anatomical Main Group.

Anatomical Main Group	Number of Medications (%)			
	Total	Withdrawal	Readministration	Continue
Cardiovascular System	787 (37.8)	583 (74.1)	122 (20.9)	204 (25.9)
Nervous System	520 (25.0)	336 (64.6)	66 (19.6)	184 (35.4)
Alimentary Tract And Metabolism	358 (17.2)	275 (76.8)	76 (27.6)	91 (25.4)
Blood and Blood Forming Organs	148 (7.1)	128 (86.5)	4 (2.7)	20 (13.5)
Genitourinary System and Sex Hormones	143 (6.9)	138 (96.5)	8 (5.8)	5 (3.5)
Systemic Hormonal Preparations, excluding sex hormones and insulin	47 (2.3)	21 (44.7)	4 (8.5)	26 (55.3)
Respiratory System	75 (3.6)	50 (66.7)	12 (16.0)	25 (33.3)
Total	2078 (100.0)	1531 (73.7)	292 (19.1)	555 (26.7)

Table 3. Management of Chronic Medication.

tients and before surgery in 6 patients. Of the 1531 drugs withdrawn in the perioperative period, 26.2 % were withdrawn for one day, 21.4 % for two days, 30.9 % for three or more days, and 21.5 % were withdrawn in the perioperative period, but the number of days is unknown. Most drugs were withdrawn in the day of surgery (35.9 %) or in the day before surgery (32.6 %). The most common medications of cardiovascular system were agents acting on renin-angiotensin system (35.9 %), lipid modifying agents (17.9 %) and diuretics (10.2 %). Of the 510 drugs for the nervous system, 40.2 % were anxyolitics and 22.3 % were antidepressants. In the group of alimentary tract and metabolism, 33.7 % were drugs used in diabetes and 23.0 % were drugs for acid related disorders. The group of blood and blood forming organs comprised exclusively antithrombotic agents (81.2 %) and antianemic preparations (18.8 %). All antithrombotic agents were withdrawn before surgery. Of the 75 drugs for respiratory system, 90.7 % were drugs for obstructive airway diseases. Of all groups of chronic medication, a low percentage (19.1 %) was readministred in the perioperative period after withdrawal, being the drugs for alimentary tract and metabolism and cardiovascular system the groups more often readministered.

A total of 332 (35.7 %) patients developed AE (intra-, postoperative, 30 days within discharge). Most intra- and postoperative AE were cardiac (77.1 %). In 23 patients were registered urgency episodes 30 days within discharge that were considered AE potentially related with chronic medication management (Table 4). Table 5 presents the incidence of all AE (intra-, postoperative and 30 days within discharge) by sex, age, ASA status, type of anesthesia, type of surgery, occupation time, chronic medication use, cardiovascular drug use, nervous system drug use and chronic medication management. There is an association between the sex and the occurrence of AE ($p = 0.000$), with a higher incidence in men. The occurrence of AE augmented with increasing age group, and there is a statistically significant association between age group and the occurrence of AE ($p = 0.000$). The rates of AE augmented with increasing ASA status, however it is not possible to apply Chi-square test. We decided to aggregate ASA I with ASA II (ASA I/II) and ASA III with ASA IV (ASA III/IV). The ASA I/II had 32.8 % AE and ASA III/IV had 50.4 % ($p = 0.000$). In the analysis of the occur-

Category	Adverse Events No (%)	
	Intra- and Postoperative	30 Days after Dicharge
Death	1 (0.2)	0 (0)
Cardiovascular System	336 (77.1)	1 (4.3)
Gastrointestinal System	2 (0.5)	2 (8.7)
Genitourinary System	3(0.7)	0 (0)
Hematologic or Vascular System	58 (13.3)	13 (56.5)
Wound	11 (2.5)	0 (0)
Metabolic/Endocrine System	2 (0.5)	0 (0)
Central Nervous System	7 (1.6)	0 (0)
Pulmonary System	16 (3.6)	0 (0)
Other	0 (0)	7 (30.5)

Table 4. Incidence of Perioperative Adverse Events Potentially Associated with Chronic Medication Management by System.

Characteristic/procedure	No [a]		Adverse Events No (%)		X^2 (p) [b]
			No	Yes	
Sex	Female	588	407 (69.2)	181 (30.8)	0.000
	Male	341	190 (55.7)	151 (44.3)	
Age (yr) Group	20-40	153	120 (78.4)	33 (21.6)	0.000
	41-60	420	297 (70.7)	123 (29.3)	
	61-80	304	162 (53.3)	142 (46.7)	
	>80	52	18 (34.6)	34 (65.4)	
ASA Status	I	156	112 (71.8)	44 (28.2)	* [c]
	II	493	324 (65.7)	169 (34.3)	
	III	128	64 (50.0)	64 (50.0)	
	IV	5	2 (40.0)	3 (60.0)	
Type of Anaesthesia	General	720	467 (64.9)	253 (35.1)	*
	Regional	191	118 (61.8)	73 (38.2)	
	Local	7	4 (57.1)	3 (42.9)	
Type of Surgery	General	415	238 (57.3)	177 (42.7)	0.000
	Gynecological	282	205 (72.7)	77 (27.3)	
	Orthopedic	89	52 (58.4)	37 (41.6)	
	Urologic	40	22 (55.0)	18 (45.0)	
	Maxillofacial	33	29 (87.9)	4 (12.1)	
	Plastic	30	26 (86.7)	4 (13.3)	
	ENT	30	16 (53.3)	14 (46.7)	
	Neurologic	10	9 (90.0)	1 (10.0)	
Occupation Time (min) Class	1-180	755	508 (67.3)	247 (32.7)	0.000
	181-360	112	57 (50.9)	55 (49.1)	
	>360	14	1 (7.1)	13 (92.9)	
Chronic Medication Use	No	267	185 (69.3)	82 (24.7)	0.042
	Yes	662	412 (69.0)	250 (37.8)	
Cardiovascular Drug Use	No	517	370 (71.6)	147 (28.4)	0.000
	Yes	412	227 (55.1)	185 (44.9)	
Nervous System Drug Use	No	658	429 (65.2)	229 (34.8)	0.354
	Yes	271	168 (62.0)	103 (38.0)	
Medication Management	Non take medication	267	185 (69.3)	82 (30.7)	0.046
	Withdrawn	595	365 (61.3)	230 (38.7)	
	Continued	67	47 (70.1)	20 (29.9)	

Table 5. Incidence of Adverse Events. [a]: Number; [b]: Chi Square (p value); [c]: It's not possible to apply Chi-Square.

Variables	Walt Statistic (p^a)	OR [b] (95 % CI [c])
Sex	5.065 (0.024)	1.489 (1.053-2.105)
Age Group	11.093 (0.001)	1.499 (1.181-1.902)
ASA Status (I/II and III/IV)	0.366(0.545)	1.143 (0.736-1.786)
Type of surgery (2 groups)	6.012 (0.014)	0.375 (0.171-0.821)
Occupation Time Class	9.862(0.002)	1.874 (1.266-2.774)
Chronic medication use	0.015(0.903)	1.056 (0.439-2.543)
Cardiovascular drug use	4.839 (0.028)	1.629 (1.055-2.516)
Chronic medication management	0.286 (0.593)	0.835 (0.431-1.618)

Table 6. Logistic Regression Analysis of Risk Factors for Developing an Adverse Event. [a]: *p* value; [b]: Odds ratio; [c]: Confidence Interval.

rence of AE by type of anaesthesia, the chi-square could not be applied, because there were few patients operated under local anaesthesia. When these were excluded from the analysis, 35.1 % patients submitted to general anaesthesia and 38.2 % submitted to regional anaesthesia had AE. There is no significant association between the type of anaesthesia and the adverse event incidence (p = 0.430). The highest frequencies of AE were observed in ENT, urologic, general and orthopedic surgeries. There is a statistically significant difference between the three groups of occupation time in the incidence of AE (p = 0.000). Patients with a longer occupation time had a higher occurrence of AE.

In the univariate analysis, the use of chronic medication was associated with the incidence of AE (p = 0.042). Regarding groups of drugs, AE were associated with cardiovascular drug use but not with nervous system drug use (Table 5). However, only cardiovascular drugs association with AE was confirmed in logistic regression analysis. For the logistic regression evaluation, was considered two groups for type of surgery, where one integrate the type of surgery with a higher incidence of AE (ENT, general, urologic, orthopaedic an gynaecological surgery) and the other the remaining. In this analysis only the variables sex, age group, occupation time class, type of surgery and cardiovascular drug use were risk factors for developing an AE (Table 6). Considering only these risk factors, taking chronic medication is still not a risk factor for AE (OR 0.908, CI 95 % 0.591-1.206).

There is a statistically significant difference in the incidence of AE between the three groups (not taking, continuing or withdrawing chronic medication) (p = 0.046). The proportions of AE are similar in groups not taking and continuing medication. Comparing the groups, two by two, there is a significant difference (p = 0.025) between the withdrawal group and the group not taking medication, however there is no difference between the continuing and the not taking medication group (p = 0.891) and none between the withdrawal and the continuing group (p = 0.159). Nevertheless, in logistic regression analysis, adjusted for sex, age group, occupation time class, type of surgery and being on cardiovascular drug, withdrawal of chronic medication was not a risk factor for incidence of adverse event (OR 0.928, CI 95 % 0.593-1.452), relatively to the not taking medication group.

Of the patients taking a cardiovascular medicine, 44.5 % suffered a cardiac AE, indicating a significant association (p = 0.000) between taking chronic cardiovascular system medication and incidence of a cardiac AE. Adjusting for, the sex, the age group, the occupation time class and type of surgery, taking cardiovascular drugs increases the risk of having cardiac AE (OR 1.715, CI 95 % 1.221-2.410). The patients, that withdrawn their cardiovascular drug, had a higher incidence of cardiovascular AE (41.7 %), than those which continued it (34.2 %). However, this is not a significant statistically difference (p = 0.221).

DISCUSSION

As previously mentioned, the majority of patients submitted to surgical procedures are on chronic medication. This study identified that 71.3 % of the patients take chronic medication (mean number of 2.4 drugs), being cardiovascular system the main therapeutic group. This study identified that, regardless from the therapeutic group, most chronic medication was withdrawn in the perioperative period. Although all antithrombotics were withdrawal, in dental and dermatologic minor procedures it is recommended to continue antithrombotic therapy with

the exception of clopidogrel [5]. The systemic hormonal preparations group was an exception. The thyroid therapy was continued in majority of patients, which was according to published recommendations [6].

The incidence of AE, after adjustment for significant confounders (sex, age group, occupation time class, type of surgery, cardiovascular system drug use), was not associated with the following variables "take chronic medication", "withdrawal versus continuing", "withdrawal *versus* not taking medication". Of the 1531 drugs withdrawn in the perioperative period, 47.6 % were suspended one or two days during the perioperative period. The withdrawal occurred in the day of the surgery or in the day before the surgery on 68.5 % of the drugs. As most patients stayed in hospital two or three days, they restarted their chronic medication on returning home. Therefore there is a possibility that a withdrawal AE is more likely to occur if the withdrawal period was longer. Since most patients took more than one drug and different withdrawal periods were identified, we decided not to analyse the association between the AE incidence and withdrawal period.

When adjusted for confounders, we found that taking a cardiovascular drug was a risk factor for the occurrence of any type of AE and, particularly, a cardiac one. Nevertheless no significant difference was observed between withdrawing and continuing the cardiovascular drug in the cardiac event incidence. These results suggest that taking a cardiovascular drug by itself is an underlying indicator of comorbidity, and therefore, of an increased potential risk of AE. In addition, the cardiovascular group includes different drug types (diuretics, beta blockers, agents acting on the renin-angiotensin system, statins) with different perioperative period management recommendations. For example, for beta-blockers and statins the recommendation is to continue during the perioperative period [7]. For diuretics and agents acting on the renin-angiotensin system the recommendation, is to withdraw before surgery, when prescribed for hypertension, but not if prescribed for ventricular failure [7]. Taking this into consideration, the analysis should have been done by subtherapeutic groups, taking into account the subjacent pathology. However, that was not an objective of the study.

Regarding the utilization of chronic medication by surgical population, our results show that 71.3 % of the patients were taking chronic medication, contrasting with the 49 % reported by Kennedy and colleagues [2].

When comparing the results reported by Kennedy and colleagues with ours, the only significant similarity is the acknowledgement that taking cardiovascular medicine is a major risk in the occurrence of cardiac AE. This may be partially explained by methodological differences. In the Kennedy and colleagues study, patients admitted for emergency surgery were included, which, according to Ingraham and colleagues, increases by itself the risk of perioperative AE [8]. In addition, complications/AE definition used was different. We analysed the medical record and Kennedy and colleagues used surgical audit and case studies. For these authors, the case studies used provide the most compelling supporting evidence for the conclusion that "withdrawal chronic medication may add significant risk to the surgery". The statistical analysis was also conducted differently: we did not categorise age and we did not evaluate being without postoperatively drugs by oral route more than 24 h as a risk factor to AE.

In our study taking a cardiovascular drug is a risk factor for the occurrence of a cardiac adverse event. However, the variable "taking chronic medication" was not identified as a risk factor for perioperative adverse events, and withdrawal/continuing of chronic medication has no impact on perioperative adverse events. In addition, since the recommendations for the management of chronic medication in perioperative period are different for pharmacological subgroups, the analysis of withdrawal or continuation as risk factors should be done accordingly. This component was not evaluated.

In addition to the limitations already mentioned, we would like to emphasize other constrictions. Being a retrospective study, based only on medical records, without a specific registry for AE, the causality of withdrawal/continuation of chronic medication and adverse events was not possible to evaluate. Information bias may have occurred, since the same reviewer identified both withdrawn drugs and AE from records. This being the case the reviewer might have looked more thoroughly for AE in these files, than in those of patients who did not withdrawn. As a consequence, AE are most likely overestimated in withdrawal group.

Further studies, with a prospective methodology and evaluating specific pharmacological

subgroups, regarding the impact of management of chronic medication in perioperative adverse events are needed.

CONCLUSION

In summary, although our work provides evidence that chronic medication and its management, either continuing or the withdrawal of it, may not add significant risk to perioperative period, it identifies the need for record keeping improvements and the further institutional collaborate studies.

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Capítulo 5

Discussão

O consenso formal definiu 23 NOC para a gestão da medicação crónica no período perioperatório. Contudo, relativamente às recomendações para a terapêutica hormonal de substituição (THS) e para os anti-inflamatórios não esteróides (AINES) não houve consenso entre os especialistas. Alguns especialistas defendem a suspensão da THS, devido ao elevado risco de tromboembolismo (Miller *et al*. 2002). Contudo, a evidência extrapolada de um estudo coorte (Nussmeier *et al*. 2005) e de um estudo caso-controlo (Hurbanek *et al*. 2004) recomenda a continuação desta medicação no período perioperatório. Relativamente aos AINES, estão publicadas cinco recomendações que sugerem que devem ser suspensos antes da cirurgia de acordo com a sua semi-vida (Ashraf *et al*. 2004), (Cohn S *et al*. 2006), (Mercado *et al*. 2003), (Kuwajerwala NK 2006), (Pass *et al*. 2004). Estas recomendações justificam-se pelos efeitos antiplaquetários dos AINES, que podem contribuir para aumentar o risco de hemorragia na cirurgia (Horlocker *et al*. 1990). Apesar dos inibidores seletivos da ciclooxigenase 2 terem um efeito mínimo na atividade plaquetária, o que poderia favorecer a utilização destes AINES no período perioperatório, têm como reação secundária a disfunção renal (Ashraf *et al*. 2004), (Cohn S *et al*. 2006), (Pass *et al*. 2004). Adicionalmente, na reunião do consenso formal, considerou-se não ser coerente suspender os AINES antes da cirurgia, pois após a mesma é comum administrá-los para controlo da dor.

Os grupos terapêuticos bloqueadores beta, estatinas e antitrombóticos não foram abordados no âmbito do consenso de especialistas, pois existem NOC publicadas para estes fármacos com classificação da recomendação e do nível de evidência (Fleisher *et al*. 2007),(Douketis *et al*. 2008).

Segundo a classificação do *Scottish Intercollegiate Guidelines Network*, das 23 NOC definidas pelo consenso, 2 foram classificadas com o grau C e 21 com o grau D (Scottish Intercollegiate Guidelines Network 2002). Ou seja, as NOC definidas são suportadas principalmente pela opinião/experiência dos especialistas, pela extrapolação de resultados de estudos classificados com 2^+ e por casos clínicos. Este nível de recomendação resulta do facto de existirem poucos estudos nesta área. Idealmente as NOC deveriam ser suportadas por meta-análises e ensaios clínicos randomizados. Todavia limitar o desenvolvimento de NOC apenas a áreas em que são feitos ensaios clínicos randomizados seria reduzir a possibilidade de melhorar a qualidade dos cuidados de saúde. De facto, nem todas as questões permitem a realização de ensaios clínicos randomizados, principalmente devido a aspetos éticos. Contudo

em todos as áreas dos cuidados de saúde é importante existirem recomendações, mesmo que sejam suportadas apenas pela experiência de especialistas na área.

A definição de NOC através de uma revisão sistemática e de um consenso de especialistas teve como objetivo transpor o conhecimento científico dos estudos existentes para a prática clínica, integrando também a experiência dos especialistas portugueses. Numa segunda fase, as NOC seriam utilizadas para determinar se os doentes em que estas eram aplicadas tinham menor risco de AA. Contudo, esta determinação não foi possível, pois em média cada doente tomava 2.4 medicamentos. Assim sendo alguns doentes tomavam 2 ou mais medicamentos do mesmo grupo terapêutico, pelo que por vezes para um medicamento as NOC eram seguidas, mas para o outro não. Outro fator que não permitiu esta análise foi o facto de o mesmo medicamento, em doentes diferentes, ter períodos de suspensão distintos. Desta forma, os dados que se obtiveram no estudo coorte eram muito heterogéneos, o que não permitiu o agrupamento de dados num número significativo para completar a análise.

No nosso estudo coorte identificou-se que 71.3% dos doentes submetidos a cirurgia tomavam medicação crónica, em média 2.4 medicamentos por doente. Dos doentes que tomavam medicação crónica, 62.1% faziam terapêutica para o sistema cardiovascular. Estes dados são semelhantes aos resultados do estudo efetuado por Kennedy *et al.*, em que se verificou que 49% dos doentes tomavam medicação crónica, em média 2.4 medicamentos por doente, sendo que a maioria dos doentes também tomavam medicação para problemas cardiovasculares (Kennedy *et al*. 2000).

No nosso estudo, verificou-se que a maioria dos doentes (89.9%) suspendeu a medicação crónica no período perioperatório, independentemente do grupo terapêutico. É de referir, que os antitrombóticos foram suspensos em todos os doentes, embora nas pequenas cirurgias de dermatologia e estomatologia seja recomendado continuar esta terapêutica no período perioperatório, com a exceção do clopidogrel (Douketis *et al*. 2008). Neste grupo de doentes, não foi registado nenhum AA tromboembólico, tendo sido feita a substituição por enoxaparina no período perioperatório em 73.3% dos doentes. A terapêutica para a tiróide foi a única medicação que foi continuada na maioria dos doentes, o que está de acordo com as NOC definidas pelo consenso de especialistas.

Ainda no nosso estudo, verificámos que a maioria dos medicamentos (47.6%) foi suspensa um ou dois dias durante o período perioperatório. Em 68.5% dos medicamentos, a suspensão foi feita no dia antes ou no próprio dia da cirurgia, sendo que apenas 19.1% dos medicamentos foram readministrados no período de internamento, provavelmente devido ao facto de a maioria dos doentes (70.5%) ter estado internado 2 ou 3 dias, tendo retomado a medicação crónica após a alta.

Na análise que efetuámos determinou-se que a toma de terapêutica cardiovascular, é um fator de risco para a ocorrência de qualquer tipo de AA, particularmente um AA cardíaco.

Contudo, não foram observadas diferenças significativas entre suspender ou continuar a terapêutica cardiovascular na incidência de um AA cardíaco. Estes resultados sugerem que tomar terapêutica cardiovascular, por si só é um indicador de comorbilidade, aumentando o potencial risco de AA. Também no estudo do Kennedy *et al*. a toma de terapêutica cardiovascular foi determinada como fator de risco para a ocorrência de complicações clínicas de carácter geral (Kennedy *et al*. 2000).

A incidência de AA, após o ajustamento para variáveis de confundimento (sexo, idade, o grupo de tempo de ocupação no bloco, tipo de cirurgia e utilização de medicação para o sistema cardiovascular) não está associada às seguintes variáveis "tomar medicação crónica", "suspensão versus continuar", "suspender versus não tomar medicação crónica". Contudo, Kennedy *et al*. determinou que tomar um medicamento não relacionado com a cirurgia está a associado a risco acrescido de 2.7 de complicações no pós-operatório, quando comparado com doentes que não tomam medicação, sendo que 5% dos doentes sofreram complicações diretamente relacionadas com a suspensão da medicação crónica no período perioperatório (Kennedy *et al*. 2000). Existem algumas diferenças de metodologia dos estudos que poderão explicar parte da divergência de resultados, nomeadamente o facto do estudo de Kennedy e colegas ter incluído cirurgias de emergência, o que aumenta o risco de AA no período perioperatório (Ingraham *et al*. 2011). Adicionalmente, a definição de AA/complicações utilizada foi diferente nos dois estudos. Kennedy *et al* utilizaram a auditoria cirúrgica e análise de casos clínicos, sendo que a auditoria cirúrgica era realizada por uma equipa médica em que todas as complicações clinicamente relevantes eram registadas e os casos clínicos eram detalhadamente registados quando havia suspeita de as complicações estarem especificamente relacionadas com a suspensão da medicação. Já no CHCB, no processo clínico em papel, não há nenhum documento específico para preencher aquando a ocorrência de complicações e os processos clínicos são muito sintéticos, não apresentando muitos detalhes, mesmo perante a ocorrência de complicações. Trata-se de duas metodologias distintas – uma pró-ativa e outra de carácter retrospetivo, condicionada pelas razões já indicadas, o que, por sua vez, limita a análise e interpretação dos resultados.

Com o objetivo de identificar AA ocorridos após a alta hospitalar foram analisadas as admissões nas urgências para todos os doentes intervencionados nos 30 dias após a respetiva alta médica. Contudo o registo informático do motivo de admissão na urgência, na maioria das vezes, reportava apenas o motivo segundo a triagem de *Manchester*, apresentando uma história clínica muito reduzida.

Assim, por ausência de registos, ou registos incompletos, pelo facto de não ter sido possível obter autorização para consultar os processos informáticos, a incidência de AA associados à gestão da medicação crónica no período perioperatório estará, inevitavelmente, subestimado. Desta forma, contrariamente ao que era esperado, o nosso estudo determinou que tomar

medicação crónica e suspender a respetiva medicação no período perioperatório não são fatores de risco para a ocorrência de AA.

Para além da dificuldade de determinar a incidência de AA, alguns processos clínicos não tinham todos os dados preenchidos. Foi identificado que os registos de 15.8% dos doentes não apresentavam a classificação ASA, 1.2% não especificava o tipo de anestesia e 5.2% não tinham informação sobre o tempo de ocupação. Outra das limitações do processo clínico cirúrgico, foi o facto de não estarem registados as patologias crónicas do doente, pelo que não foi possível utilizar este dado na análise efetuada. Desta forma, pode-se afirmar que a qualidade dos registos no processo clínico foi uma das grandes limitações do estudo. O processo clínico do doente é um conjunto de documentos que contem informação clínica e administrativa, que suporta a comunicação e o processo de decisão clínica no dia-a-dia, permite a comunicação entre os vários profissionais de saúde e entre o presente e o passado (Cruz-Correia 2009). Assim é evidente que a qualidade da informação do mesmo tem implicação direta na qualidade da prestação de cuidados de saúde (Cruz-Correia 2009). Nos dias de hoje, com a crescente preocupação com a melhoria da qualidade dos cuidados de saúde e com a diminuição de acontecimentos adversos, é fundamental melhorar a qualidade dos registos do processo clínico.

É de referir, que o ideal para avaliar se a suspensão/continuação de medicação crónica no período perioperatório tem impacto nos AA e se o risco de AA é menor quando se aplica NOC, seria realizar uma análise estratificada por subgrupos terapêuticos (bloqueadores beta, diuréticos…), em vez de grupos terapêuticos (terapêutica cardiovascular, sistema nervoso…). Esta análise não foi possível, pois a estratificação em grupos de doentes que tomassem exclusivamente um determinado grupo terapêutico resultou num número de doentes reduzido por grupo. Outra opção era fazer grupos de doentes que tomassem exatamente a mesma medicação dentro do mesmo grupo terapêutico, ou seja os doentes que tomassem bloqueadores beta e diuréticos num grupo, os doentes que tomassem bloqueadores dos canais de cálcio e diuréticos noutro grupo. Contudo, para um mesmo doente verificou-se que, por vezes, para um medicamento a NOC era seguida e para outro não.

Como já foi referido, a análise dos dados do estudo coorte deveria ser feita por grupos subterapêuticos, considerando a patologia subjacente. Contudo só foi possível efetuar esta análise para os modificadores do eixo renina-angiotensina (MERA). Vários estudos sugerem que os doentes que tomam os MERA no dia da cirurgia têm maior risco de ter episódios de hipotensão durante a cirurgia (Brabant *et al*. 1999; Brabant *et al*. 1999; Barber *et al*. 2001; Bertrand *et al*. 2001; Comfere *et al*. 2005). Por este motivo, a NOC definida no consenso de especialistas recomenda a suspensão dos MERA na manhã da cirurgia (Castanheira *et al*. 2011). A Sociedade Europeia de Cardiologia e a Sociedade Europeia de Anestesiologia também recomendam a suspensão dos MERA nos doentes hipertensos antes de uma cirurgia não cardíaca. Contudo recomendam a continuação dos mesmos nos doentes estáveis com

disfunção do ventrículo esquerdo (Poldermans *et al*. 2009). Neste estudo, avaliou-se a incidência de episódios de hipotensão e hipertensão, entre os 589 doentes que não tomavam antihipertensores e os 176 doentes que tomavam MERA (inibidores da enzima de conversão da angiotensina e antagonistas dos recetores da angiotensina) simples (o comprimido só tinha um princípio ativo) ou em combinação (com diuréticos ou bloqueadores de canais de cálcio). A mesma análise comparativa foi feita para os doentes que suspenderam os MERA antes ou no dia da cirurgia, relativamente aos doentes que tomaram os MERA até ao dia da cirurgia, inclusive. Os resultados obtidos mostraram que os doentes que tomavam MERA apresentavam maior risco de ter episódios de hipertensão durante a cirurgia em relação aos doentes que não tomavam antihipertensores (*OR 1.91, 95% CI 1.04-3.50*), quando ajustado para os fatores de confundimento. Este resultado era esperado, dado que os MERA são muito utilizados no tratamento da hipertensão. Contudo, como os dados recolhidos não nos indicavam sobre qual a patologia para qual o doente tomava o fármaco, não foi possível introduzir este dado na análise efetuada. Por outro lado, não se verificou uma diferença estatisticamente significativa na incidência de episódios de hipotensão durante a cirurgia entre os dois grupos acima referidos e entre o grupo de doentes que suspendeu comparativamente aos que continuaram os MERA até ao dia da cirurgia. Estes resultados são consistentes com dois estudos em que se compararam os utilizadores dos MERA com não utilizadores e em que se verificou que o número de doentes que necessitaram de vasoconstritores não é significativamente diferente ente os dois grupos. Contudo, uma meta-análise sugere que os doentes que tomam MERA no dia da cirurgia têm maior risco (risco relativo 1.50, 95% CI 1.15-1.96) de desenvolver episódios de hipotensão com necessidade de administração de vasoconstritores (Rosenman *et al*. 2008). Esta meta-análise é constituída por 5 estudos que apresentam diferenças evidentes na qualidade do desenho do estudo, sendo que o limite inferior do intervalo de confiança a 95% do risco relativo é muito próximo de 1, o que sugere que não é um efeito pronunciado. O facto de não existir uma diferença significativa no risco de hipotensão entre o grupo que não toma antihipertensores e o grupo de que toma MERA e entre o grupo que suspendeu a terapêutica *versus* o grupo que a continuou no período perioperatório é biologicamente plausível. Isto porque, os anestésicos, os analgésicos utilizados no intra-operatório e a própria cirurgia têm um potente efeito hipotensor, o qual pode predominar em relação à administração dos MERA.

Importa ainda referir que, adicionalmente às limitações acima discutidas, pode ter ocorrido um viés de informação, pois o investigador que identificou a medicação que foi suspensa/continuada foi o mesmo que avaliou os AA nos processos clínicos. Assim sendo pode ter acontecido que o investigador tenha tido mais atenção na identificação dos AA nos processos dos doentes que suspenderam a medicação, em relação aos que continuaram, tendo como consequência a sobrestimação dos AA no grupo de doentes que suspendeu a medicação crónica no período perioperatório.

Capítulo 6

Conclusões Gerais e Perspetivas para o Futuro

O presente trabalho consistiu na realização de um atividade de consenso de especialistas para definir NOC baseadas na evidência para a gestão do risco iatrogénico no período perioperatório e de um estudo coorte retrospetivo para a caracterização e avaliação da gestão da medicação crónica no período perioperatório.

O consenso de especialistas definiu 23 NOC para a gestão da medicação crónica no período perioperatório, para os seguintes grupos terapêuticos: bloqueadores de canais de cálcio, inibidores da enzima de conversão da angiotensina, antagonistas dos recetores da angiotensina, nitratos, diuréticos, agonistas alfa 2, digoxina, niacina, fibratos, colestiramina, colestipol, contracetivos orais, antidepressivos tricíclicos, inibidores da recaptação da serotonina, inibidores da monoamino oxidase, insulina, hipoglicemiantes orais, hormonas da tiróide, antitiróideus e glucocorticóides. A aplicação da metodologia descrita por Rycroft-Malone mostrou ser um método prático e útil para integrar diferentes formas de evidência clínica na definição das NOC (Rycroft-Malone 2001). Apesar das limitações que condicionaram o seu desenvolvimento, já referidas na discussão, admitimos que os resultados apresentados constituem uma importante contribuição para a gestão da medicação crónica no período perioperatório.

No estudo coorte verificou-se que a maioria dos doentes submetidos a cirurgia faz medicação crónica e que a sua utilização é, em regra, suspensa no período perioperatório. Contudo a toma de medicação crónica e a sua gestão (suspensão/continuação) no período perioperatório não aumenta o risco de AA no mesmo. Porém, como já foi referido, este estudo teve muitas limitações, nomeadamente no acesso e na recolha de dados. Assim, uma das principais conclusões do estudo é que é absolutamente necessário melhorar a qualidade dos dados registados no processo clínico cirúrgico. Importa ainda sublinhar a necessidade de o CHCB, enquanto hospital universitário, criar condições para que os investigadores, devidamente credenciados, tenham acesso a dados relevantes. Acreditamos que a solução passa pela criação de um sistema de acesso aos dados informáticos que permita exclusivamente a consulta de dados e não a sua modificação, com o compromisso claro do investigador respeitar a confidencialidade dos mesmos e que tal se integra perfeitamente na estratégia de melhoria da qualidade e segurança dos doentes apanágio dos processos de acreditação que o CHCB promove.

Apesar das limitações identificadas no estudo coorte, considerou-se que este trabalho contribui para o conhecimento da farmacoepidemiologia da medicação crónica no doente cirúrgico.

Com base nos resultados obtidos e nas limitações sentidas na realização do trabalho, identificaram-se algumas linhas de orientação para investigações futuras. Assim, o ideal será a realização de um estudo de coorte prospetivo com a devida colaboração dos médicos que acompanham os doentes no período perioperatório. Os dados devem ser recolhidos na avaliação clínica diária, a qual é parte integrante dos procedimentos no período de internamento, devendo os mesmos ser registados em formulário específico, em vez de utilizar o processo clínico tradicional. Para avaliar os AA que ocorram no período após internamento hospitalar propõe-se que o médico que efetuou a primeira consulta de seguimento pós-operatório preencha um formulário onde se encontram listados os principais AA associados à gestão da mediação crónica no período perioperatório. Outro aspeto que merece reflexão é o facto de se ter concluído que os doentes cirúrgicos tomam em média 2.4 medicamentos, por vezes do mesmo grupo terapêutico. Assim o ideal seria a realização do estudo em vários hospitais, para que aquando da estratificação seja possível a obtenção de grupos com um número significativo de observações. Contudo, com base na experiência resultante deste estudo, prevê-se que tal seja difícil de concretizar. No entanto, tendo como conceito primordial que todos os doentes merecem os melhores cuidados, uma forma de promover a melhoraria da qualidade dos cuidados prestados é integrar esta prática no dia-a-dia da prestação dos mesmos. Neste âmbito seria uma contribuição importante a realização de avaliações que poderia seguir o modelo de auditorias internas, nomeadamente aos seguintes pontos: verificar se formulário que é preenchido pelo anestesista tem registado as patologias crónicas e a medicação crónica do doente (princípio ativo, dose, número de tomas); verificar se as normas de orientação clínica para a gestão da medicação crónica no período perioperatório relativamente aos bloqueadores beta e às estatinas, adotadas pela Sociedade Europeia de Cardiologia e pela Sociedade Europeia de Anestesias são aplicadas (Poldermans *et al*. 2009). Também seria importante introduzir no protocolo existente para a profilaxia da doença tromboembólica venosa do CHCB nos doentes submetidos a cirurgia, as NOC publicadas para a gestão da terapêutica antitrombótica crónica.

A gestão da medicação no período perioperatório é uma atividade clínica da maior relevância que requer procedimentos complexos, baseados em orientações terapêuticas individualizadas, associadas a registos clínicos sistemáticos. Requer ainda seguimento adequado tendo em vista a avaliação, análise e correção de eventuais AA. Estas atividades pressupõem o desenvolvimento e organização de modelos de melhoria da qualidade que, não só promovam a segurança dos doentes como caracterizem e quantifiquem os referidos AA, processo que se enquadra em modelos de vigilância epidemiológica, hoje em dia indispensáveis à prática clínica.

Capítulo 7

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Capítulo 8

Resumos Publicados em Revistas com Arbitragem

8.1 Resumo I

Castanheira L, Fresco P, Macedo AF. Drug Usage Profile of Portuguese Surgical. *Basic & Clinical Pharmacology & Toxicology*; 2009; 105: 93.9th Congress of the European Association for Clinical Pharmacology and Therapeutics, 12-15 July 2009, Edinburgh, UK
http://onlinelibrary.wiley.com/doi/10.1111/pto.2009.105.issue-s1/issuetoc

8.2 Resumo II

Castanheira L; Fresco P; Macedo AF. Management of cardiovascular medication in surgical patients: indications in summary of product characteristics and substitution for intravenous forms. *Basic & Clinical Pharmacology & Toxicology* 2010; 107: 220. 16th World Congress of Basic and Clinical Pharmacology, 17-23 July 2010, Copenhagen, Denmark
http://onlinelibrary.wiley.com/doi/10.1111/pto.2010.107.issue-s1/issuetoc

8.3 Resumo III

Castanheira L, Calheiros J. Calcium channel blockers and hemostasis disorders in surgery. *Basic & Clinical Pharmacology & Toxicology* 2011;109:142. 10th Congress of the European Association for Clinical Pharmacology and Therapeutics, 26-29 June 2011, Budapest, Hungary
http://onlinelibrary.wiley.com/doi/10.1111/pto.2011.109.issue-s1/issuetoc

8.4 Resumo IV

Castanheira L, Calheiros J. Calcium channel blockers and hemostasis disorders in surgery. *Basic & Clinical Pharmacology & Toxicology* 2011;109:142. 10th Congress of the European Association for Clinical Pharmacology and Therapeutics, 26-29 June 2011, Budapest, Hungary
http://onlinelibrary.wiley.com/doi/10.1111/pto.2011.109.issue-s1/issuetoc

8.1 Resumo I

was given by 25% of participants. DS were used by 82% (2.61 ± 1.69 DS/subject; range: 1–9), mainly aminoacids (42.1%) proteins (26.2%), creatine (12.1%), vitamins (7.5%) and fluid replacements drinks (6.5%), weight control (2.8%) and energy drinks (2.8%). DS were usually purchased at specialized shops (51.2%) and in gymnasium (26.8%), upon advice from trainers (68.2%) rather than from physicians (14.6%) or pharmacists (7.3%). Expected benefits were 'quicker physical/improved performance' (63.4%); 'muscular hypertrophy' (31.7%) and were generally perceived as satisfied (80.5%). Age, sex, education, place of residence seemed not associated with use/attitudes towards DS. Use of DS was higher in bodybuilding than in other disciplines (3.6 ± 2.5 vs. 1.5 ± 1.3 DS/subject; $P < 0.05$).
Conclusion: DS appear quite popular and perceived as useful and harmless among this sample of non-professional athletes, especially in bodybuilders. We now plan to increase the surveyed population and to investigate the possible relationship between DS use and use of frankly illicit performance-enhancing/doping agents.

TP34
ANABOLIC SUBSTANCES AND BODYBUILDERS: KNOWLEDGE AND ATTITUDES, A PILOT STUDY

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Introduction: Illicit use of anabolic substances (AS) among bodybuilders seems a widespread though hidden phenomenon. We aimed to survey knowledge and risk perception related to AS use among bodybuilders.
Subjects and Methods: A pilot study was performed among non-professional bodybuilders in Northern Italy; surveyed subjects were given a semi-structured questionnaire. Other selected bodybuilders admitting the use of AS underwent anonymous interview.
Results: Thirty-one subjects (83.9% males; age [mean ± SD]: 29.2 ± 11.8 years) completed the questionnaire. Satisfactory definition of AS was given by 85.1% of respondents (87.1%). 54.8% of the subjects (100% males; $P < 0.03$ vs. females) were able to name one or more AS. Main sources of information were internet (54.8%) and trainer (45.2%), rather than physician (6.5%). All the subjects were aware of potential adverse drug reactions (ADRs). However, in a list of 23 AS-related ADRs, only 9 ± 5.2 were indicated by the subjects (mainly: sexual dysfunctions, 80.6%; myocardial infarction, 74.2%; hepatotoxicity, 70.9%). Although none declared AS use, 93.5% of participants declared it was a widespread habit. According to anonymous interviews with 7 AS users, AS-related information came from trainer/acquaintances (5) or internet (2). Four out 7 were aware of dangers (sexual dysfunctions, 100%; hepatic and cardiovascular disorders, 75%), while 3 minimized the risks. Expected benefits (increased strength/muscular mass) were satisfied and ADR occurrence (muscular injury) was declared by one subject only.
Conclusion: Results confirm the widespread interest among bodybuilders in AS. AS-related risk perception seems, however, selective and limited. Gathered information will support educational intervention.

TP35
PATTERN OF MEDICINES CONSUMPTION IN A PORTUGUESE POPULATION OF ADULTS

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According to WHO the pattern of use of medicines in a community contributes to identify their main pathologies, as well as to know the way that populations use therapeutic resources. Main objective of this work was to characterize the pattern of medicines consumption in adults enrolled in Primary Care in Health Center of Ferreira do Zêzere. It took place a traverse cohort study of level II. Sampling type it was no probabilistic. To collect data a questionnaire was applied in a sample of 361 individuals, with ages among 19 and 64 years old. The sample studied is in majority composed by females, between 46 and 55 years old, they possess basic qualifications, with a low income, and reasonable health. Consumption of medicines was declared by 61.5% of those inquired individuals, which consumed in majority among 1 to 2 medicines and most of them was revealed among the groups of higher ages, females, individuals with lower qualifications and with worse self-perception of health. Pharmacological groups more used were the painkillers and antipyretics and NSAID's. Drugs for cardiovascular and central nervous system presented relationship with age group, academic qualifications and self-perception of health. Prevalence of medicines consumption was similar to found in other studies. Like this, characterization of pattern of medicines consumption in this population can contribute, not only for a better knowledge about the health, but also for elaboration of educational programs in order to achieve rational use of medicine in this community and in all similar populations.

TP36
DRUG USAGE PROFILE OF PORTUGUESE SURGICAL PATIENTS

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Introduction: Surgical treatment of disease has a substantial unrecognized impact on health care. Definition of drug usage profiles in the perioperative period is critically needed for an efficient iatrogenic risk management. The purpose of this study was to identify the drug use profile of surgical patients at a Portuguese University Hospital.
Patients and Methods: During 1 month, a survey was applied to all adult patients consecutively admitted for elective surgery at the Cova da Beira Hospital Center (CBHC). Three separate sets of data were collected: demographic characteristics, clinical history and medication use.
Results: A total of 140 patients, 40.7% men and 59.3% women, with a mean age of 58 years old (range 18–89), were included in this study. More than 60% of the patients had at least one chronic disease, mainly hypertension (60%) and diabetes (20%). The majority of patients (71.5%) were taking regular medication (drugs/patient mean 2.6; range 0–14), for cardiovascular disorders (53%), nervous system disorders (33%) and antithrombotic therapy (25%).
Conclusion: At present, the surgical patient is a challenge for anaesthesiology. The majority of patients surveyed has at least one chronic disease and take regular medication. Additional assessment of drug perioperative complications is urgently needed for surgical therapeutic management.

TP37
ANTIBIOTICS UTILIZATION ON THE GYNECOLOGY AND OBSTETRICS CLINIC OF CLINICAL CENTER VOJVODINA

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It is well established that fetal development may be influenced by exposure in utero to chemicals, including some drugs. The reports from various countries around the world show that drug use in pregnancy is widespread; the most commonly used medicinal products are antacids, analgesics and antibiotics. The aim of this study was to examine utilization of antibiotics during and after pregnancy in women of Vojvodina. The data for this study were collected as part of the 'Dose Regimen of Antibacterial Drugs in the Function of Pharmacodynamic parameters' project. The primary source of information obtained from the mothers was via questionnaires designed to collect data from period of pregnancy, delivery and early puerperium. The analysis was surveyed on the Gynecology&Obstetrics Clinic of Clinical Center Vojvodina during the year 2007, where 423 pregnant women were included. The results showed that one woman used doxycycline in first trimester of pregnancy. Two of

 Basic & Clinical Pharmacology & Toxicology, **105** (Suppl. 1), 44–150

8.2 Resumo II

It is well established that liposomal formulations significantly increase the safety of doxorubicin without compromising the antitumor efficacy of this agent. The innovator liposomal doxorubicin is Caelyx (Doxil in USA). A generic formulation, Doxopeg, is presently commercialized in Latin America, although no information is available regarding its biopharmaceutical properties. Hence, we decided to comparatively study Doxopeg and Caelyx. Six vials were studied per formulation. Each vial contained 20 mg doxorubicin in 10 ml, according to the label. Doxorubicin content in Caelyx and Doxopeg was within the 95-105% range of the labeled dose and no impurities were detected. In the two products, at least 99.5% of doxorubicin content was encapsulated in liposomes. Both formulations were similar when examined by electron microscopy and liposomes exhibited a mean diameter of 100 nm, as determined by light scattering. However, atomic force microscopy revealed a more stable liposomal membrane in Caelyx, suggesting differences in lipid composition between formulations. Doxorubicin release rate in human plasma at 37 degrees in 24 h was about 1% of the liposomal content of Caelyx, being consistent with previous reports. On the other hand, doxorubicin release from Doxopeg was three times faster, likely due to differences in the liposomal membrane. Since doxorubicin release rate is critical for antitumor efficacy, it is concluded that Caelyx and Doxopeg are not equivalent formulations. In the absence of data on the impact of faster liposomal doxorubicin release on clinical efficacy and safety, the therapeutic use of Doxopeg is not recommended.

Paper No.: 1033
FOCUSED CONFERENCE GROUP:
P04 - PHARMACOEPIDEMIOLOGY, CURRENT CONTROVERSIES AND OPPORTUNITIES
MANAGEMENT OF CARDIOVASCULAR MEDICATION IN SURGICAL PATIENTS: INDICATIONS IN SUMMARY OF PRODUCT CHARACTERISTICS AND SUBSTITUTION FOR INTRAVENOUS FORMS

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Introduction: Each year, millions of patients around the world undergo surgical procedures. The majority of Portuguese surgical patients (71.5%) were taking regular medication, namely for cardiovascular disorders (53%). Recommendations for management of regular medication in perioperative period and the availability of intravenous forms of drugs are critically needed for an efficient iatrogenic risk management. The purpose of this study was to identify information in summary of product characteristics for management of cardiovascular medication in perioperative period and the availability of these medications in intravenous form. Materials/Patients: Summary of product characteristics of cardiovascular medication was screened for information about drug management in the perioperative period. Additionally, it was verified, for the same drugs, if an intravenous form was available to use in the perioperative period. Results: Of 46 summary of product characteristics screened, 33% had information about its use in the perioperative period and 13% had intravenous forms available. Conclusions: For the majority of cardiovascular medications, the summary of product characteristics is not enough to support the management of these medications in the perioperative period. Proper pharmaceutical formulations for cardiovascular drugs, namely intravenous, are lacking to use in surgical patients.

Paper No.: 2673
FOCUSED CONFERENCE GROUP: P17 - NEW APPROACHES AND TARGETS IN PSYCHIATRY
NEUROPLASTIC CHANGES PRECEDE CHRONIC ANTIDEPRESSANT RESPONSES OF THE 5-HT4 RECEPTOR AGONIST RS67333

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It has been recently suggested that activation of 5-HT4 receptors might possess antidepressant properties in rats after a 3 days treatment, indicating a new strategy for developing faster-acting antidepressants. In this regard, here we have evaluated in rat brain the expression of proteins related to neuroplasticity after a subacute RS67333 treatment and their correlate on behavioural paradigms. A 3-days treatment with RS67333 (1.5 mg/kg/day), previously shown to increase neurogenesis in dentate gyrus, induced an upregulation in the expression of BDNF (% increase = 64%; $p < 0.05$) and pCREB/CREB ratio (% increase = 93%; $p < 0.01$) in the hippocampus. A significant reduction in the forced swimming test (immobility time) was also observed after 3 (% red= 27%; $p < 0.001$) and 7 (% red=29%; $P < 0.001$) days of treatment. However, in the novelty-feeding suppressed test, a validated paradigm to predict chronic antidepressant efficacy, a significant reduction in the latency to feed (% red= 49%; $p < 0.03$) was observed only after 7 days of treatment. Short-term treatment with RS67333 also failed to downregulate 5-HT4 receptor-coupled adenylate cyclase activity. Our data suggest that neural proliferation-related changes induced by antidepressants precede clinical improvement. Furthermore, when compared to data regarding classical antidepressants, our results show that the activation of 5-HT4 receptors could represent a good strategy for developing antidepressants with a minor onset of action.
Supported by: Ministerio de Ciencia e Innovación (SAF07-61862) and Fundación Alicia Koplowitz

Paper No.: 1844
FOCUSED CONFERENCE GROUP: P05 - TRANSLATIONAL SCIENCE IN THE METABOLIC SYNDROME: BASIC AND CLINICAL PHARMACOLOGY
CENTRAL INJECTION OF CDP-CHOLINE SUPPRESSES SERUM GHRELIN LEVELS WHILE IT INCREASES SERUM LEPTIN LEVELS IN RATS

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Introduction: Ghrelin and leptin are two important peptides which control food intake. Recently it was shown that CDP-choline has suppressive effect on appetite. In present study we aimed to test intracerebroventricular (icv) administration of CDP-choline on serum ghrelin, leptin, glucose and corticosterone levels in rats. Material and Methods: Male Wistar rats were used in all experiments. For repeated blood withdrawal a cannula was inserted into the left carotid artery and also a cannula was placed into the right lateral ventricule for icv injections. Rats were randomized to three treatment groups and icv CDP-choline was administered at three different doses to the groups as follows: 0.5 (n = 8), 1.0 (n = 8) and 2.0 (n = 8) µmol. Saline injected rats were used as controls. Blood samples were withdrawn before and 5th, 15th, 30th, 60th and 120th min after icv injections. Results: Baseline serum ghrelin and leptin levels were not different between groups. Intragroup analysis revealed that serum ghrelin levels were suppressed significantly at 60th min with 1µmol CDP-choline injection ($p = 0.025$) whereas serum leptin levels were increased at 60th min with 0.5, 1.0 and 2.0 µmol doses of CDP-choline ($p = 0.036$, $p = 0.012$, $p = 0.043$, respectively). Serum leptin levels were significantly higher at 120th min with 1.0 and 2.0 µmol doses of CDP-choline compared with baseline values ($p = 0.017$, $p = 0.046$, respectively). Central CDP-choline injections also induced a dose- and time dependent increase in serum glucose and corticosterone levels. Conclusions: These results suggest that central injection of CDP-choline suppress serum ghrelin levels while it increases serum leptin levels.

8.3 Resumo III

P262
PREGNANCY OUTCOME FOLLOWING MATERNAL EXPOSURE TO STATINS: A MULTICENTER PROSPECTIVE STUDY

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Introduction: Statin use for the treatment of hypercholesterolemia in women of childbearing age is increasingly common. However, published data on pregnancy outcome after exposure to statins are scarce and conflicting. This contribution addresses the safety of exposure to statins during pregnancy.
Method: In a multi-center (n = 11) observational, prospective study we compared the outcomes of 249 women exposed during the 1st trimester of pregnancy to simvastatin (n = 124), atorvastatin (n = 67), pravastatin (n = 32), rosuvastatin (n = 18), fluvastatin (n = 7) or cerivastatin (n = 1) with a control group exposed to agents known to be non-teratogenic (n = 249). The data were collected by members of the European Network of Teratology Information Services (ENTIS) during individual risk counseling between 1990 and 2009. Standardized procedures for data collection were used in each center.
Results: The difference in the rate of major birth defects between the statin-exposed group and the control group was not statistically significant (4.0% vs. 2.7% OR 1.5; 95% CI 0.5–4.5, P = 0.44). The crude rate of spontaneous abortions (12.8% vs. 7.1%, OR 1.9, 95% CI 1.0–3.6, P = 0.04) was higher in the exposed group. However, after adjustment to maternal age and gestational age at initial contact, the difference became statistically insignificant. The rate of elective pregnancy-termination (8.8% vs. 4.4%, P = 0.05) was higher and the rate of deliveries resulting in live births was significantly lower in the statin exposed group (77.9% vs. 88.4%, P = 0.002). Prematurity was more frequent in exposed pregnancies (16.1% vs. 8.5%; OR 2.1, 95% CI 1.1–3.8, P = 0.02). Nonetheless, gestational age at birth (median 39 weeks, IQR 37–40 vs. 39 weeks, IQR 38–40, P = 0.27) and birth weight (median 3280 g, IQR 2835–3590 vs. 3250 g, IQR 2880-3600, P = 0.95) did not differ between exposed and non-exposed pregnancies.
Conclusion: This study did not detect a clear teratogenic effect of statins. Its statistical power however is not sufficient to reverse the recommendation of treatment discontinuation during pregnancy. At most, the results are reassuring in case of inadvertent exposure.

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CALCIUM CHANNEL BLOCKERS AND HEMOSTASIS DISORDERS IN SURGERY

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Introduction: The calcium channel blockers (CCBs) inhibit platelet aggregation, which may increase the risk of bleeding. There is evidence that CCBs are associated with increased perioperative transfusion requirements and postoperative haemoglobin loss.
This study aimed to determine the association between the chronic use of CCBs and the composite end point, hemorrhage, need for transfusion or anemia in perioperative period.
Patients and Methods: A retrospective cohort study was conducted among the patients who underwent elective surgery in 'Cova da Beira' Hospital Center (CBHC) during 1 year. The patients that take were taking anti-inflammatory non steroid or antithrombotic agents were excluded. Two groups were evaluated, CCB users and nonusers of chronic medication.
Results: The study included 295 patients, with a mean age of 48.6 years and 51.9% were man. There was 267 nonusers of chronic medication, 28 CCBs users. Three CCBs users (10.7%) and 20 nonusers of chronic medication (7.5%) had the end point. There was no significant association between the use of CCB and the occurrence of the end point (P = 0.481).
Conclusions: The incidence of haemorrhage or the need of transfusion in perioperative period was not associated with the chronic use of CCBs.
PhD student supported by a research grant from Foundation for Science and Technology, Portugal; Grant Number: SFRH/BD/36808/2007

P264
SELECTIVE SEROTONIN REUPTAKE INHIBITOR AND HEMOSTASIS DISORDERS IN SURGERY

Castanheira L., Calheiros J.

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Introduction: The use of selective serotonin reuptake inhibitor (SSRI) has been associated with an increased bleeding tendency. An increased volume of blood loss was found during orthopedic surgery in patients using SSRIs. However, preoperative use of SSRIs was associated with need blood transfusion only in one study. These results are contradictory about the impact of a possible impaired hemostasis associated with the perioperative use of SSRIs.
This study aimed to determine the association between the perioperative use of SSRI and the composite end point, hemorrhage or need for transfusion during surgery and postoperative period.
Patients and Methods: A retrospective cohort study was conducted among the patients who underwent elective surgery in 'Cova da Beira' Hospital Center (CBHC) during 1 year. The patients that were taking anti-inflammatory non steroid or antithrombotic agents were excluded. Two groups were evaluated, nonusers of antidepressants and SSRIs users.
Results: The study included 746 patients, with a mean age of 52.3 years and 64.6% were women. There were 696 nonusers of antidepressants and 50 SSRI users. Of the SSRI users one patient (2.0%) had a haemorrhage and 41 (5.9%) of the nonusers of antidepressants had the end point. There is no statically significant difference between the two groups (P = 0.352).
Conclusions: The incidence of haemorrhage or the need of transfusion in perioperative period was not associated with the chronic use of SSRI.
Liliana Castanheira PhD student supported by a research grant from Foundation for Science and Technology, Portugal; Grant Number: SFRH/BD/36808/2007.

P265
CONSUMPTION OF DRUGS ACTING ON CARDIOVASCULAR SYSTEM IN SERBIA

Divac N., Todorovic Z., Stojanovic R., Savic Vujovic K., Nesic Z., Prostran M.

Department of Pharmacology, Clinical Pharmacology and Toxicology, School of Medicine, University of Belgrade, Belgrade, Serbia

Serbia is the 4th country in the world regarding the number of citizens aged over 65 and in 2007. Had 3rd mortality rate due to cardiovascular diseases in the world. One of the consequences of such demographic occurencies is the increase of the use of cardiovascular drugs.

8.4 Resumo IV

P262
PREGNANCY OUTCOME FOLLOWING MATERNAL EXPOSURE TO STATINS: A MULTICENTER PROSPECTIVE STUDY

Winterfeld U.[1], Panchaud A.[1], Merlob P.[2], Rothuizen L.[1], Cuppers-Maarschalkerweerd B.[3], Vial T.[4], Stephens S.[5], Clementi M.[6], De Santis M.[7], Pistelli A.[8], Berlin M.[9], Z Elefteriou M.[10], Maňáková E.[11], Buclin T.[1]

[1]STIS and Division of Clinical Pharmacology and Toxicology, University Hospital, Lausanne, Switzerland; [2]BELTIS Rabin Medical Center and Sackler School of Medicine, University of Tel-Aviv, Tel-Aviv, Israel; [3]TIS, National Institute of Public Health and Environment, Bilthoven, The Netherlands; [4]Centre Antipoison-Centre de Pharmacovigilance, Hospices Civils, Lyon, France; [5]UKTIS, Regional Drug and Therapeutics Centre, Newcastle upon Tyne, UK; [6]Servizio di Informazione Teratologica, Padova, Italy; [7]Telefono Rosso-TIS, Department of Obstetrics and Gynecology, Catholic University of Sacred Heart, Rome, Italy; [8]TIS AOU Carreggi, Florence, Italy; [9]Drug consultation-TIS, Assaf Harofeh Medical Center, Zerifin, Israel; [10]Poison Control, Bergamo, Italy; [11]CZTIS, 3rd Faculty of Medicine, Charles University, Prague, Czech Republic

Introduction: Statin use for the treatment of hypercholesterolemia in women of childbearing age is increasingly common. However, published data on pregnancy outcome after exposure to statins are scarce and conflicting. This contribution addresses the safety of exposure to statins during pregnancy.
Method: In a multi-center (n = 11) observational, prospective study we compared the outcomes of 249 women exposed during the 1st trimester of pregnancy to simvastatin (n = 124), atorvastatin (n = 67), pravastatin (n = 32), rosuvastatin (n = 18), fluvastatin (n = 7) or cerivastatin (n = 1) with a control group exposed to agents known to be non-teratogenic (n = 249). The data were collected by members of the European Network of Teratology Information Services (ENTIS) during individual risk counseling between 1990 and 2009. Standardized procedures for data collection were used in each center.
Results: The difference in the rate of major birth defects between the statin-exposed group and the control group was not statistically significant (4.0% vs. 2.7% OR 1.5; 95% CI 0.5–4.5, P = 0.44). The crude rate of spontaneous abortions (12.8% vs. 7.1%, OR 1.9, 95% CI 1.0–3.6, P = 0.04) was higher in the exposed group. However, after adjustment to maternal age and gestational age at initial contact, the difference became statistically insignificant. The rate of elective pregnancy-termination (8.8% vs. 4.4%, P = 0.05) was higher and the rate of deliveries resulting in live births was significantly lower in the statin exposed group (77.9% vs. 88.4%, P = 0.002). Prematurity was more frequent in exposed pregnancies (16.1% vs. 8.5%; OR 2.1, 95% CI 1.1–3.8, P = 0.02). Nonetheless, gestational age at birth (median 39 weeks, IQR 37–40 vs. 39 weeks, IQR 38–40, P = 0.27) and birth weight (median 3280 g, IQR 2835–3590 vs. 3250 g, IQR 2880-3600, P = 0.95) did not differ between exposed and non-exposed pregnancies.
Conclusion: This study did not detect a clear teratogenic effect of statins. Its statistical power however is not sufficient to reverse the recommendation of treatment discontinuation during pregnancy. At most, the results are reassuring in case of inadvertent exposure.

P263
CALCIUM CHANNEL BLOCKERS AND HEMOSTASIS DISORDERS IN SURGERY

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Conclusions: The incidence of haemorrhage or the need of transfusion in perioperative period was not associated with the chronic use of SSRI.
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Capítulo 9

Comunicações Orais

9.1 Comunicação Oral I

Castanheira L. Recomendações para a Gestão da Medicação Crónica no Período Perioperatório. **XV JORNADAS OFIL ESPAÑA-PORTUGAL**. Cáceres. 11 e 12 de Junho 2010.

9.2 Comunicação Oral II

Castanheira L. Evaluation of Evidence Based Therapeutic Recommendations for Iatrogenic Risk Management in the Perioperative Period. **Conferência CEF2010**. Coimbra. 28 de Setembro 2010.

ANEXOS

Anexo I

Aprovação da Comissão de Ética do CHCB

Anexo II

Formulário

Anexo III

Consentimento Informado

Anexo I

Aprovação da Comissão de Ética do CHCB

Centro Hospitalar Cova da Beira, E.P.E.

P/CA 31 JUL. 2008

ENVIADO A Centro de Investigação 31 JUL. 2008

Recebido a 29.07.08

C.H.C.B., E.P.E.
Presidente a Reunião de C.A
Em 31/JUL/2008
Despacho

PRESIDENTE DO C.A.
Dr João Casteleiro

VOGAL DO C.A.
Dra. Dulce Gomes

VOGAL DO C.A.
Dra. Fátima Noqueira

DIRECTOR CLÍNICO
Dr João Gomes

ENFERMEIRO DIRECTOR
Enf.ª João Ramalhinho

Parecer:	Despacho:

ASSUNTO: Projecto de Investigação nº51-"Gestão da Medicação Crónica no Período Perioperatório"

PARA: Exmo. Sr. Presidente do Conselho de Administração

DE: Núcleo de Investigação

N.º 58/NI

Data 25/07/2008

Em relação ao assunto em epígrafe, junto envio o pedido de autorização para a realização de um estudo subordinado ao tema, "Gestão da Medicação Crónica no Período Perioperatório" cujo investigador principal é a Dr.ª Liliana Pires Antunes Castanheira de Carreiro Mendes aluna do Doutoramento em Biomedicina da Universidade da Beira Interior, a realizar no Serviço de Anestesiologia e Cirurgia deste Centro Hospitalar.

Informo que se encontram reunidos todos os requisitos necessários de acordo com o Regulamento e Normas do Núcleo de Investigação, seguindo em anexo o parecer favorável n.º 42/2008 emitido pela Comissão de Ética.

Com os melhores cumprimentos,

P'lo Núcleo de Investigação

(Dr.ª Rosa Saraiva)

PARECER N.º 42/2008 DA COMISSÃO DE ÉTICA DO

CENTRO HOSPITALAR DA COVA DA BEIRA, EPE

Na sua reunião de 24 de Julho de 2008, esta Comissão de Ética apreciou o pedido de autorização para a realização de um projecto de Investigação subordinado ao tema "Gestão da Medicação Crónica no Período Perioperatório" – Avaliação das Recomendações Terapêuticas Baseadas na Evidência", pedido esse formulado pela Dr.ª Liliana Pires Antunes Castanheira de Carreiro Mendes aluna do Doutoramento em Biomedicina da Universidade da Beira Interior, a realizar no Serviço de Anestesiologia e Cirurgia deste Centro Hospitalar

Apreciado o projecto, concluiu esta Comissão de Ética nada ter a opor à realização do mesmo.

Covilhã, 25 de Julho de 2008

O Presidente da Comissão de Ética

(Dr. Neves da Gama)

Anexo II

Formulário

Iniciais do doente __ __ __

FORMULÁRIO

Dados do doente

Iniciais (do primeiro, segundo e último nome): __ __ __ Nº Do Processo hospitalar:_____

Data de nascimento: ___/___/_____ Sexo: M( ) F( ) Peso actual:_____Kg Altura:_____cm

Cirurgia(s) Planeada(s)_____

Data da consulta de anestesia:__/__/____ Data de internamento para a cirurgia:__ /__/____

I.Consulta de Anestesia - T_0

I.A Dados Clínicos do Doente

1.	6.
2.	7.
3.	8.
4.	9.
5.	10.

I.B Medicamentos utilizados nas 2 últimas semanas (Terapêutica Regular)

Nome comercial ou genérico	Indicação Terapêutica	Forma Farmacêutica	Dose	Frequência	Via de administração
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					
11.					
12.					
13.					
14.					
15.					

I.C Medições/Classificação

1. T.A._____/_____ mmHg **2. F.C**.___p.m. **3. ASA**____

I.D Exames Laboratoriais

1

Assinatura_____

Iniciais do doente __ __ __

I.E Recomendações Terapêuticas Para o Período Perioperatório

A.Terapêutica registada na folha do enfermeiro							
Nome Comercial ou Genérico	Alteração Efectuada	Forma Farmacêutica	Dose	Frequência	Via de administração	Início Data dd/mm Hora hh:mm	Fim Data dd/mm Hora hh:mm
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
11.							
12.							
13.							
14.							
15.							
16.							
17.							
18.							
19.							
20.							
21.							
22.							

I.F Recomendações não farmacológicas (ex: jejum, dieta líquida, etc...)

I.G Outras Observações

2

Assinatura_____

Iniciais do doente __ __ __

II. *Cirurgia* - T1

II.A Dados relativos à cirurgia

Data __/__/____

Procedimento Cirúrgico

1-Tipo:_____

2-Tempo Ocupação:__:__

3-Tipo de Anestesia _____

Medições antes do Procedimento Cirúrgico

7- PAS ____ 6- PAD___ 7- FC____

4-Diagnóstico_____

5-Intervenção_____

6-Anestesia : __:__ - __:__ D-_____

7-Cirurgia:__:__ - __:__ D-_____

6-Magnitude da Cirurgia:

Major 1 __ *Major 2* __ *Intermediate* __ *Minor* __

II.B Medicamentos utilizados no procedimento cirúrgico

Nome Comercial ou Genérico	Indicação Terapêutica	Forma Farmacêutica	Dose	Frequência	Via de administração	Início Hora hh:mm	Fim Hora hh:mm
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
11.							
12.							

II.C Medições Durante o Procedimento Cirúrgico

	a) Início		b) Fim		c) Máxima		d) Mínima	
HORA hh:mm								
1-FC								
HORA hh:mm								
2-PAS								
2-PAD								

II.D Complicações durante a cirurgia

1-Ocorreram algumas complicações durante a cirurgia? Sim__ Não__

Se **sim**, preencha o anexo I para cada complicação

3

Assinatura_____

Iniciais do doente __ __ __

III. Seguimento Pós-cirurgia

III.A Durante o período pós-operatório ocorreu alguma alteração às recomendações terapêuticas relativamente à medicação crónica ?

Sim__ Não__

Se **Sim,** preencha a tabela.

Nome Comercial ou Genérico	Indicação Terapêutica	Forma Farmacêutica	Dose	Frequência	Via de administração	Início da Toma Data dd/mm Hora hh:mm (se relevante)	Fim da Toma Data dd/mm Hora hh:mm (se relevante)
1.							
2.							
3.							
4.							
5.							

Data dd/mm/aa				
HORA hh:mm				
1-FC				
HORA hh:mm				
2-PAS				
2-PAD				

III.B Outras Observações:

III.C Data de alta clínica: __/__/__

III.D <u>Complicações no pós-operatório</u>

1-Ocorreram algumas complicações durante o pós-operatório? Sim__ Não__

Se **sim**, preencha o anexo I para cada complicação

Assinatura_____

Iniciais do doente __ __ __

ANEXO I – Preencher para cada complicação

1. Complicação

A. Descrição	B. Data de Início (dd/mm/aaaa)	D. Gravidade	E. Evolução
		□ Morte	□ Cura □ Cura com sequelas
	C. Duração	□ Pôs em perigo a vida	□ Persiste sem recuperação □ Em recuperação
		□ Motivou ou prolongou a hospitalização	□ Morte com possível relação com a complicação
		□ Outra _____	□ Morte sem relação com a complicação
		□ Não Grave	□ Desconhecida

2. Causas

☐ **Condição Clínica** ☐ **Procedimento Cirúrgico**

☐ **Continuação/Alteração da Medicação Regular no Período Perioperativo (Preencher Tabela)**

A .Nome do Medicamento					
B.Houve alguma intervenção?	Sim __ Não___	Se Sim, especifique em C			
C. Tratamento	Data dd/mm Hora hh:mm	Forma Farmacêutica	Dose	Frequência	Via de admistração
☐ Readmnistrar o medicamento	__/__ __:__				
☐ Susbstituir por outro medicamento para a mesma indicação terapêutica Medicamento: _____	__/__ __:__				
☐ Suspender o medicamento	__/__ __:__				
☐ Alterar a forma farmacêutica, posologia, via de admnistração	__/__ __:__				
☐ Tratamento específico da reacção _____					

3. Resultado da intervenção: ☐ A complicação **Melhorou** ☐ A complicação **Manteve-se**

4. Outras informações relevantes:

5

Assinatura_____

Anexo III

Consentimento Informado

Centro Hospitalar Cova da Beira, E.P.E.

INFORMAÇÃO AO DOENTE

1. Título do Estudo

Avaliação da Utilização da Medicação Crónica no Período Perioperatório

O presente documento descreve a informação necessária de que depende o seu consentimento para a participação voluntária neste projecto de investigação. Sendo este documento requisito essencial para a participação, pede-se que o leia atentamente, coloque as suas dúvidas a quem lho apresenta e, se quiser participar, assine o documento. Leve o tempo que entender necessário para examiná-lo.

2. Descrição sucinta da natureza, Objectivos e Procedimentos do estudo.

A maioria dos doentes que têm que realizar uma cirurgia toma medicamentos diariamente para os seus problemas de saúde. Assim, geralmente o doente quando vai à consulta para ser avaliado pelo anestesista é aconselhado a suspender alguns medicamentos nos dias antes da cirurgia, enquanto outros continua a tomar normalmente. Contudo, esta decisão é tomada com base na experiência dos médicos, não existem critérios definidos, sendo avaliada caso a caso pelo seu médico.

O objectivo deste estudo é avaliar se os medicamentos que o doente toma regularmente são responsáveis por complicações que ocorrem no período perioperatório (antes, durante e após a cirurgia). Para isso, cada doente vai ser observado durante o período de tempo que decorre desde o internamento antes da cirurgia até ter alta, para verificar se ocorre algum problema que resulta da utilização de medicamentos neste período.

Sede: Morada: Quinta do Alvito 6200-251 Covilhã Telefone: 275 330 000 Fax: 275 330 001
Morada: Av. Adolfo Protela 6230-288 Fundão Telefone: 275 330 000 Fax: 275 751 057

Este estudo é muito importante para que se possa identificar os medicamentos que se devem continuar e os que se devem suspender quando o doente é submetido a uma cirurgia. Assim, este estudo, permitirá prevenir e antecipar complicações no período perioperatório causadas pela toma da medicação regular.

Os investigadores assumem a responsabilidade pela confidencialidade de quaisquer dados recolhidos. A informação do doente é registada num formulário, em que se utiliza a codificação de dados de forma a garantir o anonimato.

Os dados obtidos terão o seguinte percurso e utilização:

- Serão analisados e guardados durante o período do estudo na Faculdade de Ciências da Saúde, da Universidade da Beira Interior;
- O tratamento, resultados estatísticos e eventual apresentação ou publicação dos resultados, divulgarão somente estatísticas de grupo e não qualquer tipo de informação que possa identificar os participantes;
- Só poderão ser acedidos pelos investigadores;
- Serão arquivados após a conclusão do estudo num ficheiro isolado, e destruídos passados 5 anos.

A sua participação neste estudo não envolve qualquer tipo de riscos ou custos para si; não estão igualmente previstos quaisquer tipos de gratificações ou remunerações.

3. Participação Voluntária e Direitos de Recusa da Participação ou de Abandono

Terá toda a liberdade para se recusar a participar no estudo ou retirar o seu consentimento, suspendendo a participação em qualquer momento. A participação é voluntária e a sua recusa em participar não envolverá qualquer penalização ou perda de benefícios. A recusa ou abandono não colocarão, de modo algum, em risco o direito a receber tratamento ou assistência médica, presentemente ou no futuro, nesta instituição.

4. A Quem Deve Colocar Questões Relacionadas com Este Estudo

Se subsistirem algumas dúvidas ou forem necessários esclarecimentos suplementares previamente à sua participação, poderá contactar:

Nome *Liliana Mendes*
Local Faculdade Ciências da Saúde, Universidade da Beira Interior
Telefone 963082157
e-mail / site lcastanheira@fcsaude.ubi.pt

5. Identificação completa dos Investigadores e Instituições envolvidos

Investigadores

Liliana Pires Antunes Castanheira de Carreiro Mendes
Aluna de Doutoramento. Faculdade Ciências da Saúde. Universidade da Beira Interior. (BD/SFRH/36808/2007)
lcastanheira@fcsaude.ubi.pt
Tel. 963082157

Ana Filipa Pereira Amaral de Macedo
Professora Auxiliar. Faculdade de Ciências da Saúde. Universidade da Beira Interior.
filipa@fcsaude.ubi.pt

Paula Maria Façanha da Cruz Fresco
Professora Auxiliar. Faculdade de Farmácia. Universidade do Porto.
pfresco@ff.up.pt

_____

(Assinatura legível do responsável pela investigação)

Sugerimos-lhe que conserve esta cópia do documento.

DECLARAÇÃO DE CONSENTIMENTO LIVRE E INFORMADO

Avaliação da Utilização da Medicação Crónica no Período Perioperatório

Liliana Pires Antunes Castanheira de Carreiro Mendes, farmacêutica, aluna de doutoramento da Faculdade Ciências da Saúde da Universidade da Beira Interior, a realizar um trabalho de investigação no âmbito do doutoramento em Biomedicina, subordinado ao tema " Gestão da Medicação Crónica no Período Perioperatório, Avaliação das Recomendações Terapêuticas baseadas na Evidência", vem solicitar a sua colaboração no estudo. Informo que a sua participação é voluntária, podendo desistir a qualquer momento sem que por isso venha a ser prejudicado nos cuidados de saúde prestados pelo CHCB, EPE; informo ainda que todos os dados recolhidos serão confidenciais.

Consentimento Informado
Ao assinar esta página está a confirmar o seguinte:

- Entregou esta informação
- Explicou o propósito deste trabalho
- Explicou e respondeu a todas as questões e dúvidas apresentadas pelo doente.

Liliana Pires Antunes Castanheira de Carreiro Mendes
Nome do Investigador (Legível)

_____ _____
(Assinatura do Investigador) **(Data)**

Consentimento Informado
Ao assinar esta página está a confirmar o seguinte:

- O Sr.(a) leu e compreendeu todas as informações desta informação, e teve tempo para as ponderar;
- Todas as suas questões foram respondidas satisfatoriamente;
- Se não percebeu qualquer das palavras, solicitou ao investigador que lhe fosse explicado, tendo este explicado todas as dúvidas;
- O Sr.(a) recebeu uma cópia desta informação, para a manter consigo.

Nome do Doente (Legível)

_____ _____
(Assinatura do Doente) **(Data)**

Sede: Morada: Quinta do Alvito 6200-251 Covilhã Telefone: 275 330 000 Fax: 275 330 001
Morada: Av. Adolfo Protela 6230-288 Fundão Telefone: 275 330 000 Fax: 275 751 057